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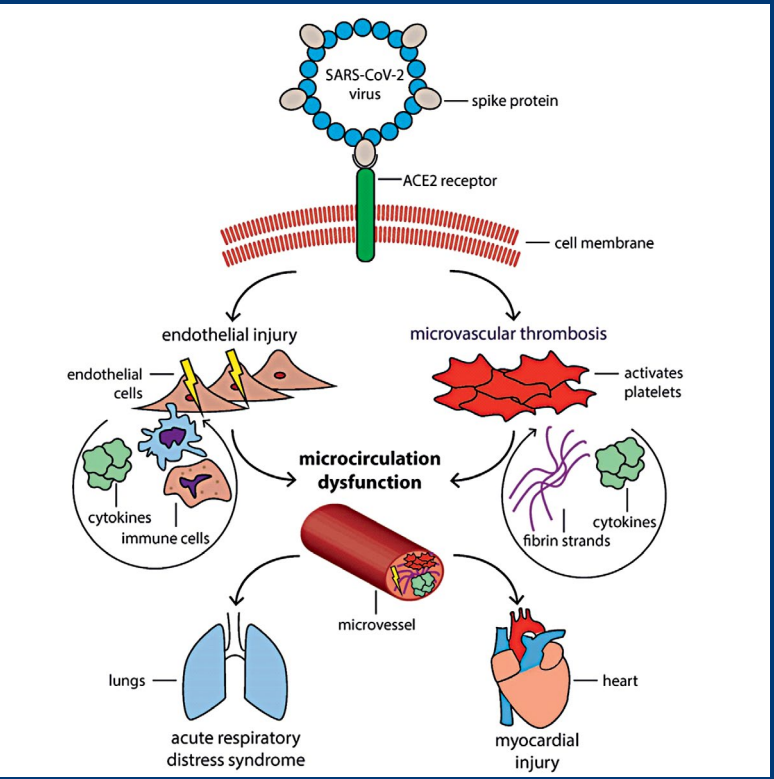

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On the search for the right definition of heart failure with preserved ejection fraction

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Abstract

The definition of heart failure with preserved ejection fraction (HFpEF) has evolved from a clinically based "diagnosis of exclusion" to definitions focused on objective evidence of diastolic dysfunction and/ /or elevated left ventricular filling pressures. Despite advances in our understanding of HFpEF pathophysiology and the development of more sophisticated imaging modalities, the diagnosis of HFpEF remains challenging, especially in the chronic setting, given that symptoms are provoked by exertion and diagnostic evaluation is largely conducted at rest. Invasive hemodynamic study, and in particular — invasive exercise testing, is considered the reference method for HFpEF diagnosis. However, its use is limited as opposed to the high number of patients with suspected HFpEF. Thus, diagnostic criteria for HFpEF should be principally based on non-invasive measurements. As no single non-invasive variable can adequately corroborate or refute the diagnosis, different combinations of clinical, echocardiographic, and/or biochemical parameters have been introduced. Recent years have brought an abundance of HFpEF definitions. Here, we present and compare four of them: 1) the 2016 European Society of Cardiology criteria for HFpEF; 2) the 2016 echocardiographic algorithm for diagnosing diastolic dysfunction; 3) the 2018 evidence-based H_2FPEF score; and 4) the most recent, 2019 Heart Failure Association HFA-PEFF algorithm. These definitions vary in their approach to diagnosis, as well as sensitivity and specificity. Further studies to validate and compare the diagnostic accuracy of HFpEF definitions are warranted. Nevertheless, it seems that the best HFpEF definition would originate from a randomized clinical trial showing a favorable effect of an intervention on prognosis in HFpEF. (Cardiol J 2020; 27, 5: 449–468)

Key words: diagnosis, diastolic function, E/e' ratio, left atrial pressure, pulmonary capillary wedge pressure, natriuretic peptides, atrial fibrillation

Introduction

Heart failure with preserved ejection fraction (HFpEF) is one of the hot topics in modern cardiology. Entering "HFpEF", "diastolic dysfunction", or related terms into the MEDLINE (Medical Literature Analysis and Retrieval System Online) database results in over 12,000 citations, with a sharp increase in recent years. Despite well-defined demographic and clinical characteristics of HFpEF patients, as well as ongoing research and discussion on the essence of HFpEF, no uniform diagnostic criteria have been widely accepted, nor has any treatment been shown to improve prognosis [1]. Different definitions have been proposed by scientific societies or adopted in randomized clinical trials [1–11]. These definitions vary greatly in their approach to the diagnosis (clinically based vs. focused on objective evidence of diastolic dysfunction and/or elevated left ventricular [LV] filling pressure, with different combinations of parameters used in each definition), which may reflect limitations of our understanding of HFpEF pathophysiology but also different stages of HFpEF continuum with some definitions aiming at preclinical diastolic dysfunction, and some directed at clinically overt, advanced HFpEF (Fig. 1) [12, 13]. In everyday clinical practice, confirming or excluding HFpEF poses a considerable challenge with a potential for both overdiagnosis (mostly in primary care and in patients hospitalized for acute dyspnea) and underdiagnosis (especially in stable, uncongested, elderly patients with exertional symptoms) [14–24]. The abundance of HFpEF definitions might cause even more confusion among non-HF specialists. This article is an attempt to present the most up-to-date diagnostic criteria for chronic HFpEF, compare different definitions, and summarize their strengths and limitations.

Why is it difficult to establish diagnostic criteria for HFpEF?

As shown in Figure 1, different diagnostic parameters reflect different pathomechanisms and different stages of HFpEF. Furthermore, most parameters are not specific for HFpEF (Table 1 [4, 24–47]). Thus, no single variable, echocardiographic or biochemical, can adequately corroborate or refute the diagnosis [4, 5]. Moreover, for different parameters, no clear cut-off points can be defined because most of them are continuously distributed within a population and may vary depending on age, gender, body surface area, body mass index (BMI), heart rhythm, kidney function, and the presence of cardiac and extra-cardiac comorbidities [5]. Notably, choosing a "lower" value as a threshold for diagnosis would increase

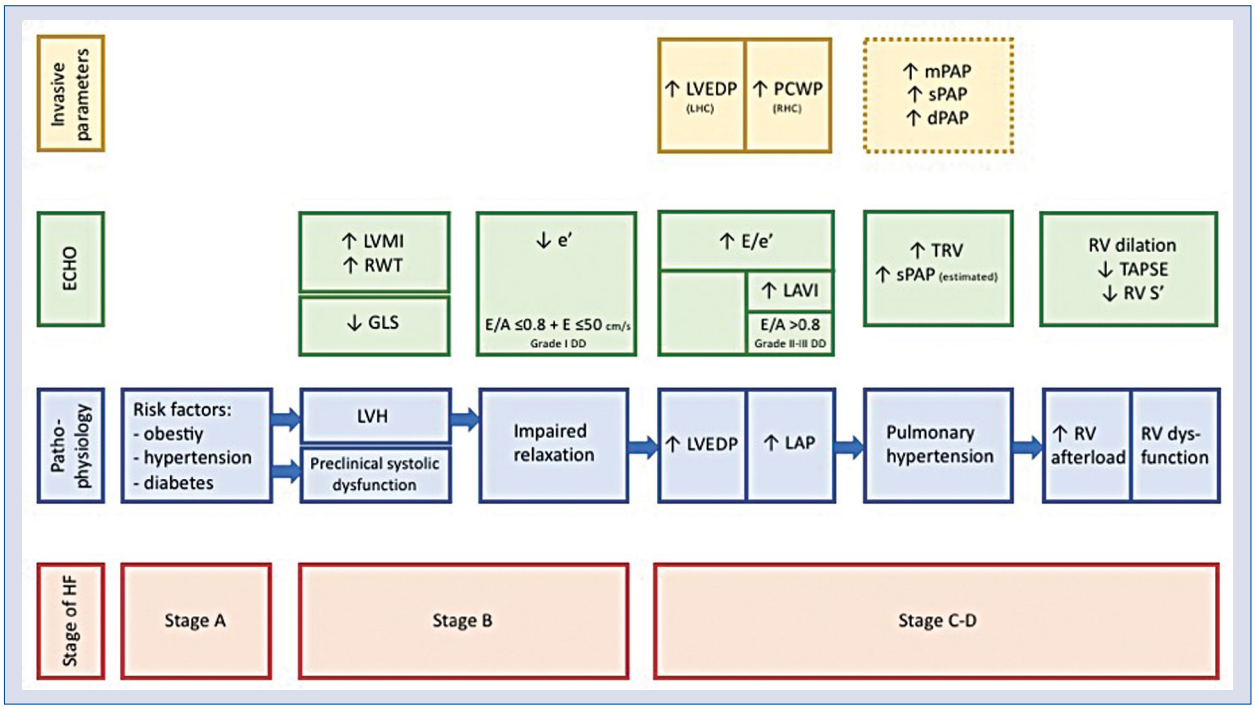

Figure 1. Natural history of heart failure with preserved ejection fraction (HFpEF) with corresponding echocardiographic and invasively measured parameters. For clarity and to enhance educational value, separate pathophysiological stages have been distinguished with parameters allocated to each stage. In reality, these stages overlap and can change with time, volume status, and level of physical activity. The diagram does not include more sophisticated echocardiographic and invasive parameters, and it does not refer to all postulated pathomechanisms (such as microvascular inflammation or cardiometabolic abnormalities). Dotted line indicates parameters (measured during right heart catheterization [RHC]) that do not constitute criteria for the diagnosis of HFpEF by any definition. Stages of HF according to the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) have been shown [2]; DD — diastolic dysfunction; dPAP — diastolic pulmonary artery pressure; GLS — global longitudinal strain; HF — heart failure; LAP — left atrial pressure; LAVI — left atrial volume index; LHC — left heart catheterization; LVEDP — left ventricular end-diastolic pressure; LVH — left ventricular hypertrophy; LVMI — left ventricular mass index; mPAP — mean pulmonary artery pressure; PCWP — pulmonary capillary wedge pressure; RV — right ventricle; RWT — relative wall thickness; sPAP — systolic pulmonary artery pressure; TAPSE — tricuspid annular plane systolic excursion; TRV — tricuspid regurgitation velocity.

Table 1. Factors affecting natriuretic peptides and chosen echocardiographic parameters assessed in the course of a diagnostic work-up for heart failure with preserved ejection fraction.

Parameter	Pathophysiologic rationale and clinical significance	Limitations and confounding factors
NPs	The main trigger for release is increased LV end-diastolic wall stress	1. In chronic HFpEF, NPs can be false negative: — NPs are more sensitive for HFrEF: LV wall stress is proportional to LV radius and inversely proportional to LV wall thickness therefore NP levels are lower in HFpEF (hypertrophic, non-dilated LV) than in HFrEF (dilated LV); LV hypertrophy in HFpEF develops to reduce wall stress — NPs are more sensitive for acute HF — Obesity and female gender are associated with lower NPs 2. NPs can be false positive in the absence of HFpEF: — Older age, AF, kidney disease, valvular heart disease, pulmonary disease, and arterial pulmonary hypertension can result in elevated NPs 3. NP levels can fluctuate in time

→

Table 1 (cont.). Factors affecting natriuretic peptides and chosen echocardiographic parameters assessed in the course of a diagnostic work-up for heart failure with preserved ejection fraction.

Parameter	Pathophysiologic rationale and clinical significance	Limitations and confounding factors
Echocardiographic parameters		
e' (septal and lateral)	e' reflects LV relaxation	— Measurement is angle-dependent — e' decreases with age — e' is unreliable in patients with mitral annular calcifications or prosthetic valves or rings — e' can be influenced by regional wall motion abnormalities due to myocardial ischemia — TDI-derived parameters are much less preload-dependent than mitral inflow; however, e' may increase with increased preload, mainly in subjects with normal LV function — in healthy subjects, e' also increases with exercise-induced tachycardia
E and E/A	The E wave reflects LA-LV pressure gradient during early diastole, which depends on LA pressure and LV relaxation/LV stiffness	— E velocity is highly dependent on preload — tachycardia affects E velocity and can lead to fusion of E/A waves — E/A ratio not applicable in AF — E/A ratio is age-dependent — without additional variables normal and pseudonormal mitral inflow pattern are difficult to differentiate — increased E velocity and pseudonormal/restrictive mitral inflow pattern can be secondary to other causes, including in particular moderate-to-severe mitral regurgitation, volume overload (e.g. in kidney disease), constrictive pericarditis, etc.
E/e'	The most appropriate echocardiographic parameter reflecting LV filling pressure: — E/e' ≥ 15 has a high positive predictive value for elevated PCWP — E/e' is less dependent on: • preload than E and e' velocities • heart rate than E velocity • age than e' velocity	— Correlation with invasive measurements is moderate with a "grey zone" for intermediate values of 9–14
LAVI	Enlarged LA reflects longstanding elevation of LA pressure	— LA enlargement can be secondary to other causes, including in particular AF, mitral valve diseases, volume overload (e.g. in kidney disease), etc. (reduced specificity) — LA enlargement develops with time and can be absent at an early stage of HFpEF (reduced sensitivity)
TRV and sPAP	TRV is used for estimation of: — echocardiographic probability of pulmonary hypertension (as per 2015 ESC/ERS guidelines) — sPAP using simplified Bernoulli equation: sPAP = 4 × TRV^2 + estimated right atrial pressure	— Correlation with invasive measurements is moderate — TRV measurement may be difficult or impossible (e.g. in the case of absent or trivial tricuspid regurgitation or suboptimal acoustic window) — TRV and echocardiographically estimated sPAP increase with age — TRV is preload dependent — increase in TRV and sPAP can be secondary to other causes, including left heart disease other than HFpEF, pulmonary disease, pulmonary embolism and chronic thromboembolic pulmonary hypertension, pulmonary arterial hypertension, fluid overload, etc. — massive TR can result in low systolic RV-RA pressure gradient (low TRV) leading to underestimation of sPAP

Based on references: [4, 24–47]. AF — atrial fibrillation; ERS — European Respiratory Society; ESC — European Society of Cardiology; HF — heart failure; HFpEF — heart failure with preserved ejection fraction; HFrEF — heart failure with reduced ejection fraction; LA — left atrium; LV — left ventricle; NP — natriuretic peptide; PCWP — pulmonary capillary wedge pressure; RA — right atrium; RV — right ventricle; sPAP — systolic pulmonary artery pressure; TDI — tissue Doppler imaging; TR — tricuspid regurgitation; TRV — tricuspid regurgitation velocity

sensitivity at the expense of lower specificity, while setting a "higher" threshold would increase specificity at the expense of lower sensitivity. Thus, establishing cut-offs for echocardiographic variables and natriuretic peptides (NPs), though based on comparisons with invasive measurements, is inevitably arbitrary. The above considerations regarding adoption of cut-off points refer even to the "gold standard" of HFpEF diagnosis — heart catheterization [48, 49]. Invasive hemodynamic assessment is considered a reference investigation for diagnosing HFpEF [5, 12, 28]. However, it has limited availability compared to the large number of patients requiring diagnostic evaluation for this highly prevalent disease. Other limitations include unknown reproducibility and a questionable risk/benefit ratio of an invasive study in view of the lack of specific HFpEF treatment [12, 49]. Hence, ideally, in most patients, diagnosis should be made based on non-invasive testing. However, validation of NPs and echocardiographic indices of HFpEF shows their relatively poor correlation with invasive hemodynamic measurements [4, 24–30, 39, 44–46, 50]. Among different echocardiographic variables, the E/e' ratio is considered the most appropriate for approximation of LV filling pressures, but its agreement with invasive measurements is only moderate [24–30]. Similarly, echocardiographic estimation of pulmonary artery pressure is not very accurate compared to right heart catheterization (RHC) [44–46]. This, again, explains the need for an algorithm including a combination of different non-invasive variables rather than a single parameter to diagnose HFpEF.

Another problem is that NP concentrations as well as echocardiographic indices of diastolic function and left atrial (LA) pressure can change in time, and therefore a single measurement of a given parameter does not provide definitive conclusions. Repeated measurements of NPs can show up to 100% variability in concentration in an individual patient [5, 40]. Mitral inflow velocities, tricuspid regurgitation velocity (TRV), and to a lesser extent LA volume index (LAVI) and e' velocities can also change over time depending on preload and/or heart rate [31–34, 41–47]. Another issue regarding echocardiographic measurements would be intra- and interobserver variability [51–53]. Importantly, in chronic HFpEF, symptoms are observed during physical exertion, and thus measurements obtained at rest can lead to false negative results. Most non-invasive HFpEF definitions refer to assessment at rest with the possibility to proceed to exercise echocardiography if the results are inconclusive or if the risk is deemed intermediate [1, 4, 5]. Notably, when invasive exercise testing was implemented as a reference method, among patients finally diagnosed with HFpEF, almost half displayed elevation in pulmonary capillary wedge pressure (PCWP) only during exercise [24, 54]. This indicates that even the "gold standard" of HFpEF diagnosis, invasive hemodynamic study, can yield a high proportion of false negative results if performed only at rest.

The aforementioned problems are mirrored by a relatively poor agreement between different HFpEF diagnostic criteria: a patient diagnosed with HFpEF according to one definition, may be reclassified as not having HFpEF according to another [19, 21–24, 55]. Moreover, non-invasive HFpEF definitions vary significantly in their accuracy in identifying patients with invasively proven HFpEF, as well as in their predictive value for future cardiovascular events [19, 20–24, 55]. It seems that the best "validation" of a HFpEF definition would be a positive result of a randomized clinical trial showing a favorable effect of an intervention on prognosis in HFpEF — inclusion criteria in such a trial could automatically become diagnostic criteria for HFpEF.

The first step towards a modern definition: The 2016 ESC guidelines

The 2016 European Society of Cardiology (ESC) HF guidelines were revolutionary by distinguishing three clinical syndromes: HF with reduced (HFrEF), preserved (HFpEF), and mid-range ejection fraction (EF), with an unequivocal definition of each of these clinical entities [1]. The diagnosis of chronic HFpEF in a patient with an EF of ≥ 50% required the presence of HF symptoms and/or signs, elevation of NPs (B-type NP [BNP] ≥ 35 pg/mL or N-terminal pro-BNP [NT-proBNP] ≥ 125 pg/mL), and at least one of the following echocardiographic criteria: LA enlargement (LAVI > 34 mL/m^2), LV hypertrophy (by LV mass index [LVMI]), or diastolic dysfunction (by E/e' ratio and e') [1]. Given the low specificity of LA enlargement and NP exclusionary cut-off points adopted in the guidelines, those criteria could be perceived as relatively "mild" with some potential for overdiagnosis. However, it seems reasonable for a new definition to include a wider spectrum of patients facilitating their accurate characterization and a thorough analysis to identify more specific subgroups. On the other hand, the definition itself was based on assessment at rest, which, in patients

with exertional symptoms, may have led to false negative results. In fact, in well compensated patients with HFpEF confirmed by invasive exercise testing, its sensitivity was found to be only 60% and specificity 75% [24].

An echocardiographic algorithm for the diagnosis of diastolic dysfunction: The 2016 ASE/EACVI recommendations

In 2016, less than two months after the release of the ESC guidelines on HF, the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI) published recommendations on the echocardiographic evaluation of diastolic function (an update of a previous document from 2009) [4, 56]. A simple algorithm was proposed for echocardiographic assessment of diastolic function in patients with an EF of ≥ 50% (Fig. 2A). The algorithm was based on four easily obtainable echocardiographic parameters: two tissue Doppler imaging (TDI)-derived, direct indices of LV diastolic dysfunction (reduced e' velocity and increased E/e' ratio) and two "indirect" parameters secondary to elevation of LA pressure (increased LAVI and TRV) [4]. Compared to the ESC guidelines, the ASE/EACVI algorithm did not account for LV hypertrophy nor, understandably, NP concentrations. Nevertheless, it was more specific for diastolic dysfunction, due to the requirement of three or four positive criteria to satisfy the definition, compared to only one positive echocardiographic criterion required to meet the ESC definition [1, 4, 24]. The ASE/EACVI algorithm also enabled echocardiographic estimation of LA pressure and grading of diastolic dysfunction based largely on mitral inflow pattern (Fig. 2B) [4]. In patients with dyspnea and grade I diastolic dysfunction (normal estimated LA pressure at rest), exercise echocardiography was recommended [4]. Importantly, the ASE/EACVI algorithm is the only one among the four discussed in this document which is designed for identifying and grading diastolic dysfunction rather than diagnosing HFpEF as a clinical syndrome.

The ASE/EACVI algorithm was validated against invasive measurements in a few studies, with sensitivity for elevation of resting LV filling pressures ranging from 69% to 87% and specificity ranging from 74% to 88%, which was significantly superior to clinical assessment [21–23]. However, when validated against invasive exercise testing, its sensitivity dropped to 34% (maintaining a high specificity of 83%) [24].

Evidence-based assessment of HFpEF probability: The 2018 H_2FPEF score

Contrary to other HFpEF definitions based on expert consensus opinion, the H_2FPEF score was derived from a cohort of 414 patients with an EF of ≥ 50%, who were referred for exercise RHC for unexplained dyspnea in Mayo Clinic (Rochester, MN, USA) [54]. The H_2FPEF score includes six dichotomized, widely available variables (four clinical and two echocardiographic), which, if positive, are attributed one point, with the exception of atrial fibrillation (AF) and obesity (BMI of > 30 kg/m^2), which are attributed three and two points, respectively (Table 2). Thus, the maximum score is nine points. For each score, the probability of invasively confirmed HFpEF was calculated, allowing justifiable exclusion of HFpEF in patients with total scores of 0–1, and establishing its diagnosis with reasonably high confidence (likelihood of > 90%) at scores of 6–9 [54].

In the original study, the H_2FPEF score proved superior to the 2016 ESC definition, allowing accurate discrimination of HFpEF from noncardiac causes of dyspnea with area under the curve (AUC) in the receiver operating characteristic (ROC) analysis of 0.84 and 0.89 in the derivation and validation cohort, respectively [54]. Interestingly, inclusion of NT-proBNP cut-off points did not incrementally add diagnostic ability to the score [54]. This again confirms that, contrary to acute symptom exacerbation, in ambulatory patients with stable, exertional dyspnea, the discriminative value of NP measurements for HFpEF is relatively low because chronic HFpEF patients may have low NP concentrations, and patients with normal LV diastolic function can have elevated NPs due to AF or other comorbidities [35–40].

In subsequent studies, the H_2FPEF score showed high sensitivity for clinically ascertained diagnosis of HFpEF, as well as predictive value for future HF-related events both in HFpEF and in non-HF patients with cardiovascular risk factors [57–60].

A comprehensive, stepwise approach to diagnosis: The 2019 HFA-PEFF algorithm

In 2019, the Heart Failure Association (HFA) of the ESC released a consensus recommendation for the diagnosis of HFpEF [5]. The proposed HFA-PEFF algorithm, presented in Figure 3, is a stepwise approach, including:

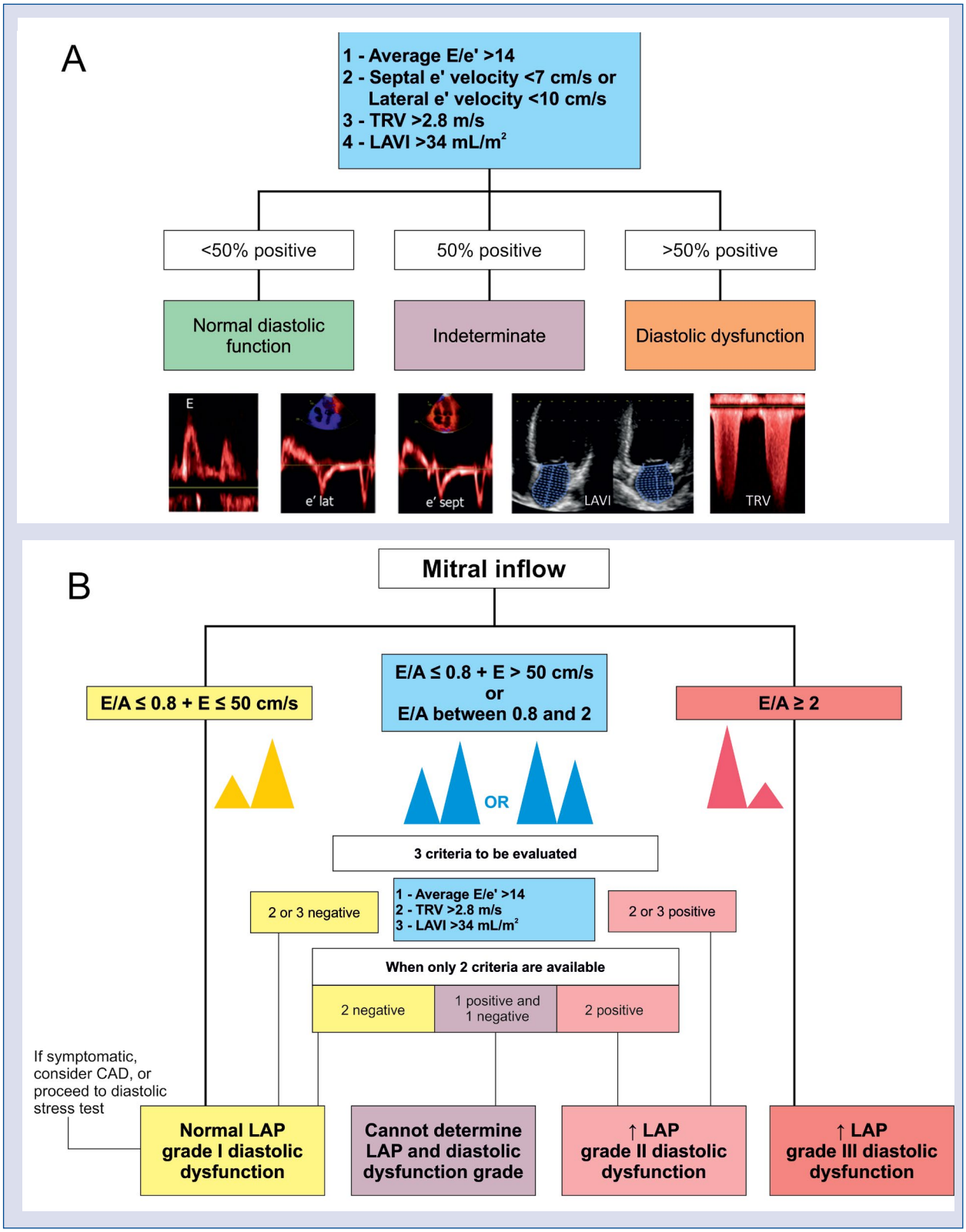

Figure 2. The 2016 American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/ /EACVI) diagnostic algorithm for: **A.** The diagnosis of diastolic dysfunction in patients with preserved ejection fraction, **B.** Grading of diastolic dysfunction and estimation of left atrial pressure (LAP) in patients with preserved ejection fraction and myocardial disease. Adopted from Nagueh et al., 2016 [4], modified; CAD — coronary artery disease; LAVI — left atrial volume index; TRV — tricuspid regurgitation velocity.

Table 2. The H_2FPEF score. Adopted from Reddy et al., 2018 [54], modified.

	Clinical variable	Value	Points
H_2	**H**eavy	BMI > 30 kg/m^2	2
	Hypertensive	2 or more antihypertensive medicines	1
F	Atrial **F**ibrillation	Paroxysmal or persistent	3
P	**P**ulmonary Hypertension	sPAP > 35 mmHg*	1
E	**E**lder	Age > 60 years	1
F	**F**illing Pressure	E/e' > 9*	1
H_2FPEF score			**Sum: 0–9**

*From Doppler echocardiography; BMI — body mass index; sPAP — systolic pulmonary artery pressure

— step 1 — **P** for **P**retest assessment;
— step 2 — **E** for **E**chocardiographic and NP score;
— step 3 — $\mathbf{F_1}$ for **F**unctional testing in case of uncertainty;
— step 4 — $\mathbf{F_2}$ for **F**inal etiology.

Step 1 (P): Pretest assessment

This step is consistent with an initial diagnostic work-up of patients presenting with dyspnea or other symptoms suggestive of HF, as recommended by the 2016 ESC guidelines on HF [1, 5]. Its goal is to identify individuals with potential diagnosis of HFpEF and exclude (or identify) alternative causes of symptoms (such as HFrEF, valvular disease, coronary artery disease, arrhythmias, pulmonary disease, anemia, etc.). This step encompasses clinical assessment, laboratory tests (including NPs if available), electrocardiogram, chest X-ray, and standard echocardiography. Clinical assessment includes evaluation of symptoms as well as risk factors for HFpEF (older age, obesity, arterial hypertension, metabolic syndrome with prediabetes/diabetes) and coexisting conditions. On the one hand, some comorbidities may imitate HF symptoms, and on the other hand, some are highly prevalent in HFpEF and thus strongly suggestive of HFpEF, even if they could themselves explain exertional dyspnea (obesity, AF). If NP measurement is available, lower cut-off points (BNP of 35 pg/mL or NT-proBNP of 125 pg/mL, consistent with the 2016 ESC guidelines on HF) are adopted in step 1 due to their higher sensitivity and negative predictive value [1, 5]. Still, almost one fifth of patients with invasively proven HFpEF had NT-proBNP below this threshold, and thus normal NP concentrations do not exclude chronic HFpEF, especially in obese patients [24, 35–40]. Standard echocardiography aims to exclude alternative cardiac causes of dyspnea, assess EF (with "preserved EF" defined as ≥ 50%), and identify features suggestive of HFpEF, such as nondilated LV with concentric remodeling or hypertrophy, and LA enlargement. If step 1 (P) indicates possible HFpEF, then step 2 (E) is indicated [5].

Step 2 (E): Echocardiographic and NP score

Step 2 is based on the HFA-PEFF scoring system with 0–2 points assigned for each of the three domains: 1) functional (echocardiography), 2) morphological (echocardiography or, less frequently, cardiac magnetic resonance), and 3) biomarker (NPs). In each domain, cut-offs for certain parameters have been proposed and attributed one (minor criterion) or two points (major criterion), as shown in Table 3. Importantly, one domain can contribute maximally two points, even if more major or minor criteria are fulfilled. A total score of 5–6 points is considered to be diagnostic for HFpEF, while a score of 0–1 points makes the diagnosis of HFpEF unlikely and should prompt assessment of other possible causes of symptoms. A score of 2–4 points requires further evaluation (step 3) using exercise testing (echocardiographic or invasive) [5].

In the HFA-PEFF score, different cut-offs for NPs and LAVI have been adopted for AF (vs. sinus rhythm), for e' for patients aged ≥ 75 years (vs. younger patients), and, similarly to the ESC definition, for LVMI for women vs. men. For NPs, eight cut-off points are given: four for BNP and four for NT-proBNP, depending on heart rhythm (with cut-offs in AF three times higher than in sinus rhythm) and criterion type (major vs. minor) [5]. From the clinical perspective, the complexity of the score with multiple variables in each domain and diverse cut-off points for one variable might be considered a drawback hindering its use in eve-

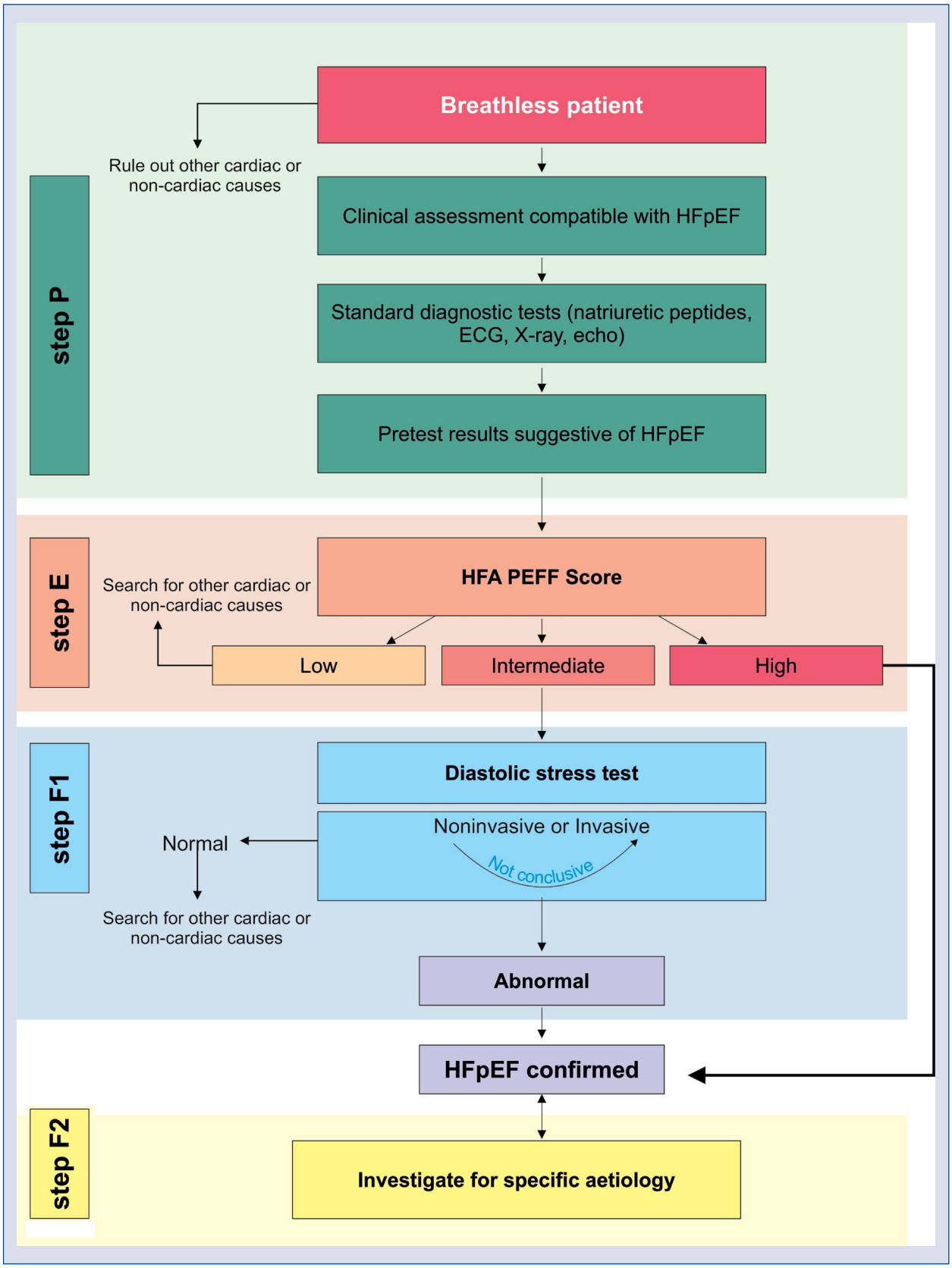

Figure 3. The HFA-PEFF diagnostic algorithm. Adopted from Pieske et al., 2019 [5], modified; HFpEF — heart failure with preserved ejection fraction; ECG — electrocardiogram.

Table 3. The HFA-PEFF score (step 2 of the HFA-PEFF algorithm). Adopted from Pieske et al., 2019 [5], modified.

	Domain		
	Functional	**Morphological**	**Biomarker**
Major: 2 points	**e':** Age < 75 years: Septal e' < 7 cm/s **or** Lateral e' < 10 cm/s Age ≥ 75 years: Septal e' < 5 cm/s **or** Lateral e' < 7 cm/s **or** **Average E/e'** ≥ 15 **or** **TRV** > 2.8 m/s (sPAP > 35 mmHg)	**LAVI:** SR > 34 mL/m^2 AF > 40 mL/m^2 **or** **RWT** > 0.42 **and LVMI:** M ≥ 149 g/m^2 W ≥ 122 g/m^2	**NT-proBNP:** SR > 220 pg/mL AF > 660 pg/mL **BNP:** SR > 80 pg/mL AF > 240 pg/mL
Minor: 1 point	**Average E/e'** 9–14 **or** **GLS** < 16%	**LAVI:** SR 29–34 mL/m^2 AF 34–40 mL/m^2 **or** **RWT** > 0.42 **or** **LVMI:** M > 115 g/m^2, < 149 g/m^2 W > 95 g/m^2, < 122 g/m^2 **or** **LV wall thickness** ≥ 12 mm	**NT-proBNP:** SR 125–220 pg/mL AF 375–660 pg/mL **BNP:** SR 35–80 pg/mL AF 105–240 pg/mL
Select only one score from each domain Total score: 0–1 points: HFpEF unlikely → search for alternative causes of symptoms 2–4 points: intermediate probability → diastolic stress test (non-invasive or invasive) 5–6 points: HFpEF confirmed			

AF — atrial fibrillation; BNP — B-type natriuretic peptide; GLS — global longitudinal strain; HFpEF — heart failure with preserved ejection fraction; LAVI — left atrial volume index; LVMI — left ventricular mass index; M — men; NT-proBNP — N-terminal proBNP; RWT — relative wall thickness; sPAP — systolic pulmonary artery pressure; SR — sinus rhythm; TRV — tricuspid regurgitation velocity; W — women

ryday practice. However, as stressed by the HFA Experts, not all parameters from each domain need to be available to calculate the score, and therefore the seeming abundance of parameters actually increases its practical utility because typically not all parameters are given in an echocardiographic report. Thus, HFpEF diagnosis actually requires only one major criterion from each domain (e.g. TRV > 2.8 m/s, LAVI > 40 mL/m^2, and NT-proBNP > 660 pg/mL for patients with AF) or two major criteria and one minor criterion (e.g. E/e' of ≥ 15, LAVI > 34 mL/m^2, and NT-proBNP 125–220 pg/mL for patients with sinus rhythm). On the other hand, a definite exclusion of HFpEF would ideally necessitate evaluation of all parameters.

Notably, the HFA-PEFF score has, for the first time, included reduced absolute global longitudinal strain (GLS), an index of impaired systolic function, as a criterion for HFpEF diagnosis. Up to two thirds of HFpEF patients show abnormal GLS despite preserved EF [61, 62]. This reflects the complexity of HFpEF pathophysiology, with preclinical systolic dysfunction as yet another contributor to HFpEF syndrome [63–65].

The HFA-PEFF score was validated in two independent studies [55, 66]. The first study included two prospective cohorts and showed excellent sensitivity (99% for low-likelihood category, i.e. a total of 0–1 points) and specificity (93% for high-likelihood category, i.e. a total of 5–6 points) of the score with an AUC of 0.90 [66]. However, final HFpEF diagnosis in this study was not based on invasive measurements but mostly on echocardiography, NPs, and clinical judgement. Furthermore, both cohorts included patients with high pre-test probability of HFpEF with only a small control group of non-HFpEF patients (potential selection bias). Notably, more than one third of patients in both cohorts were classified in the intermediate-likelihood category (a total of 2–4 points) with

a need for step 3 of the HFA-PEFF algorithm to secure the diagnosis [66]. In the second study, the HFA-PEFF score was validated against exercise testing with invasive hemodynamic monitoring, showing only moderate accuracy, with an AUC of 0.73 [55]. One quarter of patients in whom HFpEF could have been ruled out based on the HFA-PEFF score (0–1 points) had elevated PCWP consistent with HFpEF diagnosis, and almost one fifth of patients deemed to have HFpEF by the score (5–6 points) had normal PCWP both at rest and during exercise [55].

Step 3 (F_1): Functional testing in the case of uncertainty

Step 3 is performed in patients who were attributed 2–4 points in the HFA-PEFF score (step 2), and encompasses exercise echocardiography and/or heart catheterization at rest and during exercise. **Exercise echocardiography** (preferably using a semi-supine bicycle) can show an elevation in LV filling pressures (by E/e' ratio) during exertion, which can be accompanied by an increase in pulmonary artery pressure (estimated using TRV). An increase in the E/e' ratio to ≥ 15 adds two points to the HFA-PEFF score calculated in step 2. An increase in the E/e' ratio to ≥ 15 with a peak TRV of > 3.4 m/s adds three points to the HFA-PEFF score. A combined score from step 2 (E) and step 3 (F_1) of five points or more confirms HFpEF diagnosis. If the combined score does not exceed five points, **invasive hemodynamic assessment** is recommended. This includes right and/or left heart catheterization at rest, and — in the case of inconclusive results — exercise RHC. Diagnostic criteria for HFpEF include resting LV end-diastolic pressure (LVEDP) of ≥ 16 mmHg on left heart catheterization and/or mean PCWP of ≥ 15 mmHg on RHC (of note, the cut-off point for PCWP is consistent with the 2016 ESC guidelines on HF but somewhat different from the threshold for postcapillary pulmonary hypertension adopted in the 2015 ESC guidelines on pulmonary hypertension [PCWP of > 15 mmHg]) [1, 5, 46]. Given that elevation of LV filling pressure may be present only during exertion, normal resting LVEDP or PCWP do not exclude HFpEF [24, 54]. In such patients, exercise RHC using cycle ergometry is recommended, and an increase of PCWP to ≥ 25 mmHg is considered diagnostic for HFpEF [5]. The 2019 HFA consensus document does not refer to the possible role of acute volume challenge during RHC in establishing HFpEF diagnosis [46].

Step 4 (F_2): Final etiology

In most patients, HFpEF is associated with typical demographic and clinical presentation, and is related to common risk factors (older age, arterial hypertension, obesity, and metabolic syndrome), but in some patients HFpEF may be a manifestation of specific heart muscle diseases, for example hypertrophic cardiomyopathy, infiltrative cardiomyopathies (such as amyloidosis, sarcoidosis, or hemochromatosis), storage diseases (such as Fabry disease, glycogen storage diseases, or Gaucher disease), radiation-induced cardiomyopathy, endomyocardial fibrosis, autoimmune diseases, and other genetic disorders. Such specific etiologies need always to be considered, especially in cases with atypical presentation or positive family history, and if suspected, should prompt implementation of advanced diagnostic measures. Depending on the suspected underlying cause of HFpEF, these might include cardiac magnetic resonance, 99mTc-DPD scintigraphy, positron emission tomography, cardiac or non-cardiac biopsies, and/or specific laboratory tests, including genetic testing [5].

Is the 2016 ESC definition still valid?

The 2016 ESC HFpEF definition was much more liberal and less specific than the 2019 criteria adopted by the HFA. The ESC definition required only one echocardiographic criterion to be fulfilled, and cut-off points for LVMI and NPs were consistent with the 2019 HFA minor criteria [1, 5]. Thus, the 2016 ESC definition should have the advantage of higher sensitivity, and might be used for screening patients with symptoms suggestive of HF. The initial diagnostic work-up of a patient with suspected HF (including the cut-off points for NPs) proposed in the 2016 ESC HF guidelines was largely incorporated into step 1 (P) of the 2019 HFA-PEFF algorithm [1, 5].

A comparison of HFpEF diagnostic criteria from different documents is shown in Table 4.

Are the 2019 HFA-PEFF score and the 2016 ASE/EACVI algorithm compatible?

The 2016 ASE/EACVI algorithm refers to evaluation of LV diastolic function and relies purely on echocardiographic criteria [4]. On the contrary, the 2019 HFA-PEFF score was designed to diagnose HFpEF in symptomatic patients and requires both echocardiographic assessment and measurement of NPs [5]. As presented in Table 5, cut-off points for e' and the E/e' ratio in the two algorithms

Table 4. Comparison of types of criteria used to diagnose heart failure with preserved ejection fraction (HFpEF) according to different recommendations.

Criteria	HFpEF/diastolic dysfunction definition			
	2016 ESC guidelines	2016 ASE/EACVI recommendations	2018 H_2FPEF score	2019 HFA-PEFF score
Clinical	X		X	*
Echocardiographic	X	X	X	X
Natriuretic peptides	X			X

*The score is designed to diagnose HFpEF in stable, symptomatic patients. ASE — American Society of Echocardiography; EACVI — European Association of Cardiovascular Imaging; ESC — European Society of Cardiology; HFA — Heart Failure Association

Table 5. Cut-off points for tissue Doppler imaging-derived parameters and tricuspid regurgitation velocity (TRV) in different recommendations on the diagnosis of diastolic dysfunction.

Parameter	HFpEF/diastolic dysfunction definition		
	2016 ESC guidelines	2016 ASE/EACVI recommendations	2019 HFA-PEFF score
Resting echocardiography			***major criterion:***
e' lateral [cm/s]	< 10	< 10	< 10 *
e' septal [cm/s]	< 8	< 7	< 7 *
Average E/e'	≥ 13	> 14	≥ 15 **
TRV [m/s]	–	> 2.8	> 2.8
Exercise echocardiography			
Average E/e'	> 13	> 14 ***	≥ 15
TRV [m/s]	–	> 2.8	> 3.4

*For patients < 75 years; **E/e' between 9 and 14 is a minor criterion; ***or septal E/e' > 15; ASE — American Society of Echocardiography; EACVI - European Association of Cardiovascular Imaging; ESC — European Society of Cardiology; HFA — Heart Failure Association; HFpEF — heart failure with preserved ejection fraction

are comparable [4, 5]. However, given the different rules of point attribution, as well as obligatory NP measurement in the HFA-PEFF score, the two algorithms are not interchangeable, and some patients diagnosed with HFpEF/diastolic dysfunction according to one of them might not necessarily fulfil criteria allowing its unequivocal diagnosis according to the other (see examples, Fig. 4). Nonetheless, patients diagnosed with diastolic dysfunction using the ASE/EACVI algorithm will have at least intermediate probability of HFpEF in the HFA-PEFF score (because they will score at least two points). Conversely, patients with HFpEF diagnosis based on the HFA-PEFF score (5–6 points) might theoretically have normal diastolic function according to the ASE/EACVI algorithm, e.g. if they had significant LV hypertrophy with high NP concentrations (major criteria) with preserved e' velocities, low TRV, and LA that has not enlarged yet (E/e' ratio is expected to be elevated with high NPs, although this is not always the case, see Fig. 4A). However, such a scenario seems less probable in clinical practice. Comparison of the diagnostic accuracy of the two algorithms, their mutual validation, and assessment of the proportion of reclassified cases should be the aims of future studies.

With a wider spectrum of echocardiographic parameters and NP measurement, the 2019 HFA--PEFF algorithm offers a more integrated approach to the diagnosis of HFpEF, which may prove more reliable, although this still needs to be confirmed. On the other hand, apart from diagnosing diastolic dysfunction (including preclinical diastolic dysfunction), the 2016 ASE/EACVI criteria enable its grading with an estimation of LA pressure, which, although not very accurate, is very useful in clinical practice, especially for follow-up of HF patients and assessment of efficacy of diuretic treatment. Notably, this year, a modification of the 2016 ASE/ /EACVI algorithm was proposed by two of its authors, however, not as official recommendations [67].

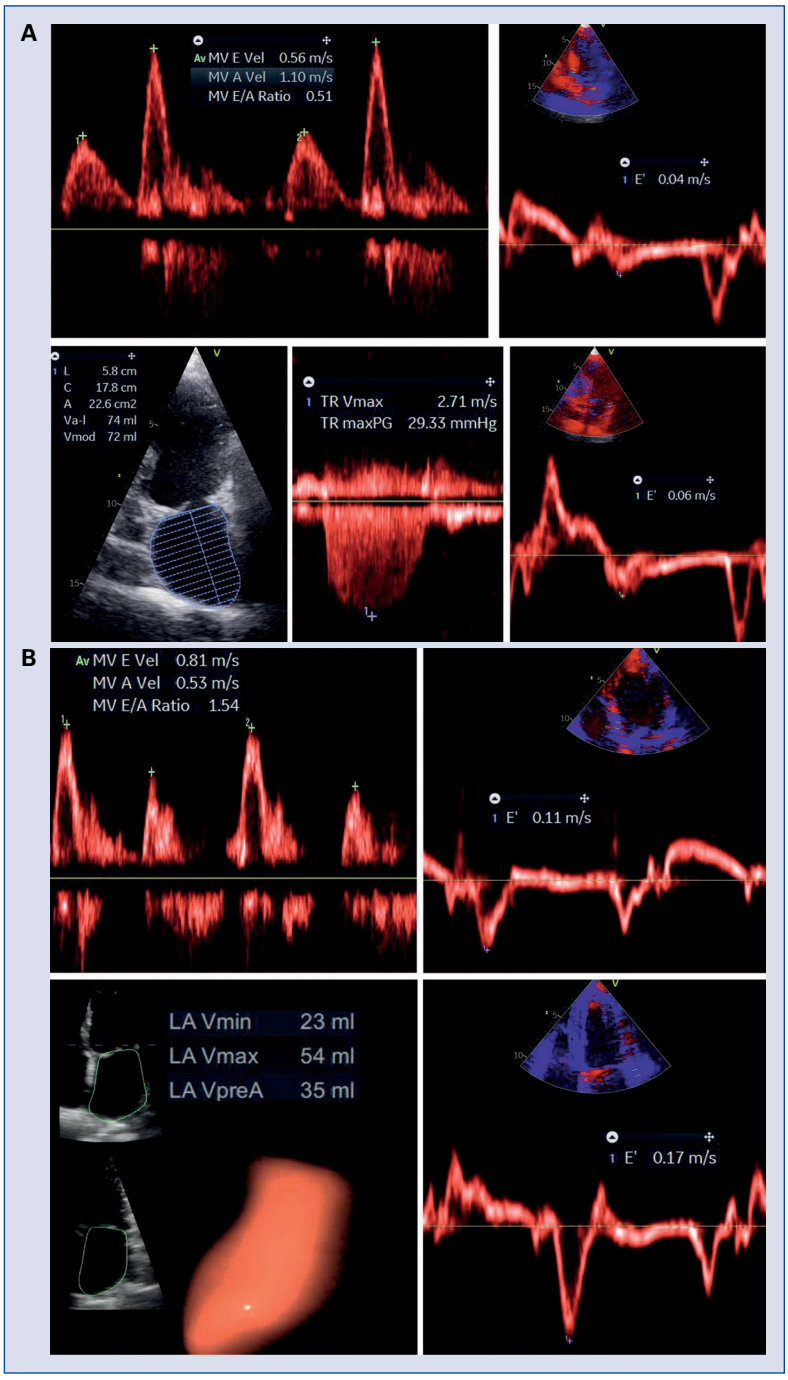

Figure 4. Comparison of the American Society of Echocardiography/European Association of Cardiovascular Imaging (ASE/EACVI) algorithm and the HFA-PEFF score based on clinical cases. **A.** An 88-year-old man with exertional dyspnea, sinus rhythm, and CCS with a history of percutaneous coronary intervention. Resting echocardiography revealed EF of 51%, LVH (LVMI 125 g/m^2, RWT 0.48), reduced e' velocities with E/e' of 11, LAVI of 40 mL/m^2, and TRV of 2.71 m/s. NT-proBNP was 371 pg/mL. Based on the ASE/EACVI algorithm, echocardiography was inconclusive for the diagnosis of diastolic dysfunction (two of four criteria positive). Given E velocity of 0.5 m/s, estimated resting LA pressure can be classified as normal; therefore, symptoms could either be attributable to CCS or would require assessment with diastolic stress test (see Fig. 2B). However, according to the HFA-PEFF score (a total of six points), the patient can be diagnosed with HFpEF without proceeding to stress test. **B.** A 51-year-old woman with sinus rhythm and exercise intolerance. Resting echocardiography revealed EF of 65%, concentric LV remodeling (LVMI 69 g/m^2, RWT 0.49), normal e' velocities with E/e' of 6, and LAVI of 33 mL/m^2 (LA volume of 54 mL, BSA of 1.64 m^2). There was no detectable TR Doppler signal profile. NT-proBNP was 338 pg/mL. Based on the ASE/EACVI algorithm, the patient was classified as having normal diastolic function. However, according to the HFA-PEFF score, with a total of three points (two points for the biomarker domain and one point for the morphological domain), HFpEF probability is intermediate, and the patient requires diastolic stress test.

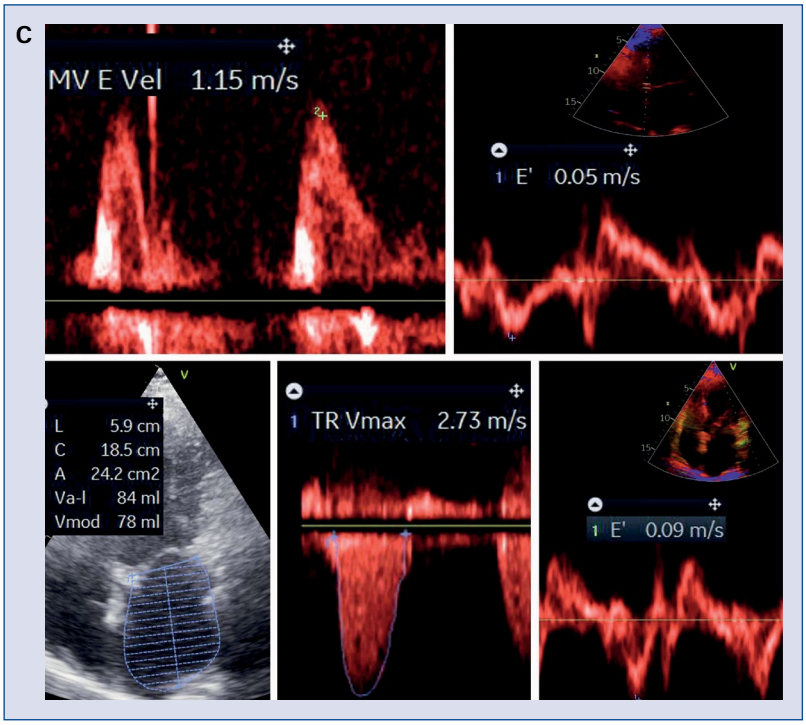

Figure 4 (cont.). C. A 75-year-old woman with atrial fibrillation. Resting echocardiography revealed EF of 57%, concentric LVH (LVMI 111 g/m^2, RWT 0.58), and e' septal and lateral of 5 and 9 cm/s, respectively (reduced as per ASE/EACVI algorithm, but within the norm range for age as per HFA-PEFF score), with E/e' of 16.4, LAVI of 42 mL/m^2, and moderate TR with TRV of 2.73 m/s. NT-proBNP was 849 pg/mL. According to the ASE/EACVI algorithm, the patient has diastolic dysfunction. This is consistent with the result of the HFA-PEFF score (six points, diagnosis of HFpEF); BSA — body surface area; CCS — chronic coronary syndrome; EF — ejection fraction; HFpEF — heart failure with preserved ejection fraction; LA — left atrium; LAVI — left atrial volume index; LV — left ventricle; LVH — left ventricular hypertrophy; LVMI — left ventricular mass index; NT-proBNP — N-terminal pro-B-type natriuretic peptide; RWT — relative wall thickness; TRV — tricuspid regurgitation velocity.

Do the European HFA-PEFF score and the American H_2FPEF score refer to the same patients?

The two definitions share similarities: both use a combination of various parameters in the form of a scoring system, and both are based on a Bayesian approach, describing HFpEF likelihood rather than providing a straightforward diagnosis. Both are meant for evaluation of chronic, symptomatic patients (the H_2FPEF score — those with unexplained dyspnea). However, there are some major differences between the two scores. First, the H_2FPEF score is an evidence-based tool derived and validated in patients referred for RHC, while the HFA-PEFF score is an expert consensus-based concept. Second, the H_2FPEF score is predominantly based on clinical profiles, while the idea behind the HFA-PEFF score is that hemodynamic abnormalities in HFpEF can and should be objectivized by echocardiography and NPs [5, 54]. Thus, the H_2FPEF score could make a convenient bedside screening tool incorporated as step 1 (P) into the HFA-PEFF algorithm. Another premise for the use of the H_2FPEF score as a screening method is its high sensitivity, resulting from the fact that almost half of the HFpEF patients in the derivation cohort had early-stage HFpEF with elevation of LV filling pressures only during exertion [54, 57]. Third, the effect of AF on the probability of HFpEF seems discordant in the two scores: in the H_2FPEF score the presence of AF significantly increases the likelihood of HFpEF, while in the HFA-PEFF score it necessitates higher cut-off points of NPs and LAVI, decreasing the probability of HFpEF diagnosis at lower values. Thus, the same patient might even be classified at the opposing ends of the spectrum of HFpEF probability by each of the two scores. An elderly patient with unexplained dyspnea, AF, and a BMI of > 30 kg/m^2 would be attributed a total of six points in the H_2FPEF score, satisfying the criteria for HFpEF, regardless of the echocardiographic result (and regardless of NP measurement, which is not required in this score) [54]. In the HFA-PEFF algorithm, such a patient would only complete step 1 (P) and would require

a thorough echocardiographic and NP assessment using the HFA-PEFF score (step 2 [E]), with higher cut-offs for NPs and LAVI due to AF [5].

A comparison of the two scores in an Asian population demonstrated high specificities of both scores (81% for the HFA-PEFF score and 88% for the H_2FPEF score) with significantly higher sensitivity of the HFA-PEFF score (74%) than of the H_2FPEF score (25%) [68]. This surprisingly low sensitivity of the H_2FPEF score might be explained by the fact that Asian HFpEF patients are almost a decade younger and have a lower prevalence of obesity and AF (two and three points in the H_2FPEF score, respectively) than their western counterparts [69]. Thus, predictive values of different scores may substantially vary depending on the population studied.

Practical considerations on clinical profiles

Analysis of the presented HFpEF definitions may lead to a few realizations regarding clinical characteristics, including female sex, obesity, and AF.

Heart failure with preserved EF is widely regarded as a disease of older women [70]. However, even though the proportion of women is higher than men in the HFpEF population (contrary to HFrEF), the incidence of HFpEF adjusted for age and other risk factors tends to be similar in women and men [16, 71–73]. Notably, female sex was not included as a criterion in any of the above presented scores or definitions [1–11, 54]. A higher proportion of women among HFpEF patients might result from their higher life expectancy [72]. However, estrogen deficiency has been postulated as one of the contributors underlying HFpEF development in post-menopausal women [74–76]. Among HFpEF patients, women have smaller LV dimensions with poorer diastolic reserve and higher LV filling pressures at rest and exercise [77].

Obesity should not be perceived as a sufficient explanation for breathlessness or low exercise capacity but as a strong risk factor of HFpEF [70, 71]. This is reflected by two points attributed for a BMI of > 30 kg/m^2 in the H_2FPEF score [54]. Importantly, obesity can lead to NP concentrations that are normal or close to normal, even in the presence of HFpEF [1, 36, 38]. Unfortunately, this was not accounted for in the HFA-PEFF score [5]. Based on observations from hemodynamic studies, the existence of a distinct, obese phenotype of HFpEF has been postulated recently [78, 79].

Atrial fibrillation is highly prevalent in HFpEF — even more prevalent than in HFrEF [16, 80, 81]. This is because AF is not only a consequence of elevation of LA pressure and LA enlargement in the course of HF (regardless of EF), but also because AF and HFpEF share a common pathophysiological background and risk factors (older age, obesity, hypertension, diabetes) [82, 83]. However, AF can also be regarded as an important confounder in diagnosing HFpEF; first, because it can lead to an increase in NPs and LAVI even in the absence of HFpEF, and second, because it hinders echocardiographic evaluation of diastolic function [5]. Thus, as mentioned above, different scores represent different approaches to AF: the more "clinical" H_2FPEF score recognizes it as a risk factor, while the HFA-PEFF score sees it as a confounding factor [5, 54].

Last but not least, even modern HFpEF definitions are, to some extent, "diagnoses of exclusion". For example, the derivation cohort for the H_2FPEF score included patients referred for RHC for "unexplained" dyspnea, i.e. after exclusion of HFrEF, valvular heart disease, pulmonary arterial hypertension, constrictive pericarditis, clinically relevant pulmonary disease, and other conditions that might have accounted for their symptoms [54]. Similarly, step 1 (P) of the HFA-PEFF algorithm assumes exclusion of other cardiac and non-cardiac causes of dyspnea [5]. This is understandable given the aforementioned low specificity of most currently available echocardiographic and biochemical parameters. Still, in the elderly, multimorbidity is highly prevalent, and even more so in patients with HFpEF [70–72]. A single patient may, and often does, have several comorbidities, apart from HFpEF, that might add to his/her symptoms, and all of them deserve recognition and treatment. Thus, validation of the presented HFpEF definitions should ideally be conducted in unselected cohorts of symptomatic patients.

HFpEF definitions in clinical trials

Table 6 presents inclusion criteria applied in major HFpEF randomized clinical trials, which are largely inconsistent with the definitions reviewed above. Those trials included also a subset of patients that we nowadays refer to as HF with mid-range EF [6–11]. Analyzing inclusion criteria in those studies, over the years, an evolution of HFpEF definition can be seen, from more clinically based to objectivized by echocardiography and NPs.

Table 6. Inclusion criteria in some major heart failure with preserved ejection fraction (HFpEF) trials.

Inclusion criteria	CHARM--Preserved 1999–2000 [6]	I-PRESERVE 2002–2005 [9]	TOPCAT 2006–2012 [8]	PARAGON-HF 2014–2016 [10]	EMPEROR--Preserved 2017–2020 [11]
Clinical criteria (HF symptoms and signs)	NYHA II–IV for at least 4 weeks	NYHA II–IV for at least 4 weeks	≥ 1 HF symptom + ≥ 1 HF sign	HF symptom(s) requiring treatment with diuretic(s) at least 30 days prior to screening visit, NYHA II–IV at screening visit	NYHA II–IV for at least 3 months
Prior hospitalization	For a cardiac reason	For HF within 6 months (not obligatory)	For HF within 12 months (alternative to elevated NPs)	For HF within 9 months (not obligatory)	For HF within 12 months (alternative to LAE/LVH)
LVEF	≥ 40%	≥ 45%	≥ 45%	≥ 45%	> 40%
Other echo-cardiographic criteria (evidence of structural heart disease)	–	LAE or LVH	–	LAE or LVH	LAE or LVH
NT-proBNP	–	–	≥ 360 pg/mL* (alternative to prior HF hospitalization within 12 months)	For pts with HF hospitalization within 9 months: — pts without AF: > 200 pg/mL, — pts with AF: > 600 pg/mL. For pts with no HF hospitalization within 9 months: — pts without AF: > 300 pg/mL, — pts with AF: > 900 pg/mL	Pts without AF: > 300 pg/mL, Pts with AF: > 900 pg/mL

*or BNP ≥ 100 pg/mL. AF — atrial fibrillation; BNP — B-type natriuretic peptide; CHARM Preserved — Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity; EMPEROR-Preserved — Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; HF — heart failure; I-PRESERVE — Irbesartan in Heart Failure and Preserved Ejection Fraction; LAE — left atrial enlargement; LVEF — left ventricular ejection fraction; LVH — left ventricular hypertrophy; NPs — natriuretic peptides; NT-proBNP — N-terminal pro-BNP; NYHA — New York Heart Association; PARAGON-HF — Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction; pts — patients; TOPCAT — Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist

Interestingly, prior HF hospitalization was (and still is) a common (although not always obligatory) criterion for inclusion, driven by the intent to recruit higher risk patients with more potential to prove benefits from treatment by event reduction. This approach also reflects the fact that HFpEF manifestation is more evident in the acute setting of symptom exacerbation, but on the other hand might have led to its overdiagnosis and loss of the effect of spironolactone on the primary endpoint in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial [8, 84]. For now, no treatment tested in clinical trials has demonstrated an improvement in survival in HFpEF, although some benefit was observed when analyzing other clinical endpoints (e.g. HF hospitalizations for candesartan, perindopril, and spironolactone) or specific HFpEF subpopulations (e.g. women for sacubitril-valsartan) [6, 8, 10, 85]. Similar to HFrEF, HFpEF is not a homogenous clinical entity, but encompasses a wide spectrum of underlying diseases ultimately leading to elevated LA pressure despite preserved EF. This heterogeneity of the HFpEF syndrome may, at least in part, account for disappointing results of clinical HFpEF trials [86]. It is postulated that the "one fits all" strategy may need to be changed to a more individualized approach based on phenotypic patient characterization including cardiac and non-cardiac comorbidities [87–91].

Conclusions: Which definition shoud we use?

The abundance of diagnostic criteria for HFpEF results from uncertainty regarding its underlying pathophysiology and lack of definition-guided treatment [1–11, 13, 54, 92]. At present, the 2019 HFA-PEFF algorithm constitutes the most comprehensive HFpEF definition, and its widespread use should be supported [5]. However, the 2016 ESC guidelines on HF can still be used in step 1 (pretest assessment) of the HFA-PEFF algorithm [1]. Alternatively, implementation of the H_2FPEF score in step 1 (P) might be advocated in patients with unexplained dyspnea, especially if NP measurements are not readily available [54]. Thus, in patients with suspected HFpEF, we suggest using the 2016 ESC HFpEF definition or estimation of HFpEF probability with the H_2FPEF score for screening purposes by general practitioners, internists, geriatricians, or general cardiologists (as step 1 [P]), and if positive, verification of diagnosis using step 2 ([E]; the HFA-PEFF score) and, when indicated, step 3 (F_1) of the HFA-PEFF algorithm by an HF specialist.

The 2016 ASE/EACVI definition was less comprehensive than the new HFA-PEFF algorithm but had an important practical advantage: it enabled echocardiographers to establish or exclude the presence of diastolic dysfunction, grade it, and summarize their conclusions in an echocardiographic report (simply the presence or absence of diastolic dysfunction at rest) [4]. This facilitated confirmation or exclusion of HFpEF diagnosis for clinicians who might not be familiarized with detailed echocardiographic indices of diastolic function. In the 2019 HFA-PEFF score, echocardiographic parameters and NP concentrations are analyzed in conjunction, which potentially leads to some confusion among non-HF specialists, hindering everyday use of the score due to its complexity [5]. Thus, in patients evaluated for dyspnea, it might be reasonable for echocardiographers to summarize the results from the two echocardiographic domains (functional and morphological) of the HFA-PEFF score by providing the total number of points (0–4 out of 4 possible) in conclusions of an echocardiographic report. The attending physician could then simply add 0–2 points depending on NP concentration to obtain the final result of the HFA-PEFF score.

Studies validating the HFA-PEFF score against invasive measurements, with comparison to the ASE/EACVI algorithm and the H_2FPEF score, are warranted. The future will show whether this HFpEF definition will hold or whether it will be replaced by new diagnostic criteria — maybe originating from a positive randomized clinical trial?

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How to diagnose? How to treat? Dilemmas of the HFpEF

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Article p. 449

Heart failure (HF) is defined as a clinical syndrome in which typical symptoms such as breathlessness, fatigue and others accompanied by signs of pulmonary and/or peripheral congestion resulting from structural and/or a functional cardiac abnormality leading to reduced cardiac output and/or elevated intracardiac pressures at rest or during exertion [1]. Clinical presentation of HF should be confirmed by transthoracic echocardiography (TTE) which reveals cardiac morphology, function and allows the calculation of ejection fraction of the left ventricle (LVEF). Low ejection fraction (EF) corroborates HF diagnosis, nevertheless in a substantial number of patients with obvious clinical HF manifestation LVEF remains within the normal range (≥ 50%). The latter group constitutes a separate category of HF patients — with preserved ejection fraction of the left ventricle (HFpEF) which differs in many aspects from those with reduced EF (HFrEF). These differences mainly include risk factors, comorbidities, patient demographics, diagnostic algorithm and evidence-based treatment.

Heart failure with preserved ejection fraction of the left ventricle has become a preponderant form of HF in western countries accounting for > 70% amongst patients > 65 years and is constantly growing with every decade of life and the gap between HFpEF and HFrEF is getting wider [2]. This is caused by growing number of obese, diabetic individuals, with metabolic syndrome living a sedentary life who are at risk of a progression to symptomatic HFpEF if left untreated. The difference in LVEF which defines both groups results from an entirely distinct cardiac pathophysiology leading to a decrease in overall ventricular performance which is described by left ventricular (LV) pressure/volume relationship. If dominant functional abnormality in HFrEF is diminished LV contractility defined by a decrease in the slope of the end-systolic pressure-volume relationship (systolic elastance), the HFpEF exhibits increase in LV diastolic stiffness causing an upward and leftward shift of the diastolic pressure-volume relationship [3]. In some individuals this may occur only on exertion. Invasive evaluation of the filling pressures remains the gold standard of diagnosing HFpEF and currently is the only method which unequivocally proves or refutes its pathophysiology.

For years HF was diagnosed on the grounds of clinical findings known as the Framingham criteria which suffer from poor sensitivity [2]. In particular, well compensated patients with HFpEF who develop symptoms only by exertion may go unrecognized. Although invasive assessment may confirm increased diastolic filling pressures during exercise this method cannot be applied as widely as required for obvious reasons. Alternatively, echocardiography is widely utilized to discover LV diastolic dysfunction. Elevation in the E/e' indicating higher LV filling pressures as well as increased estimated systolic pulmonary artery pressure represents the most robust indicators of HFpEF [4]. TTE also uncovers other structural (LV hypertrophy, higher left atrial volume) and functional (RVFAC, TAPSE) abnormalities associated with HFpEF. Recently, speckle tracking echocardiography has become a promising tool which exhibits

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subtly diminished ventricular systolic function in a subclinical phase of the disease when EF remains normal. Most of TTE parameters are specific but not sensitive enough to rule out the absence of HFpEF. American Society of Echocardiography/ /European Association of Cardiovascular Imaging recommendations provide meticulous algorithms for studying and interpreting LV diastolic performance both in patients with reduced and preserved EF. Of utmost importance is ability of echocardiography to rule out secondary HFpEF due to valvular disease, pericarditis and other conditions requiring specific diagnostic and therapeutic strategies. Further, TTE enables noninvasive evaluation during exercise which may unmask diastolic dysfunction in case of normal parameters at rest [5].

Owing to the difficulties and doubts concerning the diagnosis of the HFpEF two comprehensive diagnostic scores integrating clinical and echocardiographic variables were recently proposed in order to appreciate the risk of HFpEF. For patients with unexplained dyspnea Reddy et al. [4] developed H_2FPEF composite score which assesses the probability of HFpEF. Importantly, HFpEF as established by H_2FPEF was verified by means of invasive hemodynamic exercise testing in every patient [4]. Utilization of the score enables the Bayesian approach in which only patients with intermediate pre-test probability are referred for a definitive test including exercise testing. A similar score was proposed as a consensus expert statement (HFA-PEFF) which, thus far, has not been verified by means of invasive tests [6]. The latter score adds a concentration of N-terminal-pro--B-type natriuretic peptide, more echocardiographic morphological and functional parameters as well as exercise echocardiography. An intermediate probability is an indication for subsequent hemodynamic exercise testing.

Despite diagnostic uncertainties, many symptomatic patients worldwide are diagnosed as having HFpEF and are subsequently treated. However, contrary to HFrEF, large-scale clinical trials did not provide firm clues concerning treatment despite testing many hypotheses, drugs from various classes and non-pharmacological strategies. Considering the variety of etiologies and pathophysiologies, it seems to be justified to categorize HFpEF patients into more homogeneous phenotypes which may lead to better characterization of the entire HFpEF cohort. Various features and parameters modifying such a phenotype include comorbidities, cardiac and pulmonary vascular function, hemodynamics, extracardiac structure, function and biomarkers [2]. Obokata et al. [7] proposed obese, ischemic, and cardiometabolic phenotypes as three major categories of HFpEF pointing to essential differences among them and their preferred therapeutic options. It is conceivable that one therapeutic strategy may turn out valuable only in a given well-defined HFpEF phenotype and not in others. However, there are still many more issues to be addressed with regard to pathophysiology, definition, diagnostic algorithms and therapies since HFpEF encompasses various hemodynamic and cellular mechanisms [8]. With respect to noninvasive assessment of HFpEF, diastolic stress echocardiography remains the only tool which is capable of recognizing patients with symptoms solely with exercise. Nonetheless, a lot of effort has to be made to refine and standardize its methodology. On the other hand, simplification of a diagnostic approach should be sought for such as combination of simple TTE parameters and biomarkers as well as selection of simple highly reproducible parameters used for community based epidemiological studies and screening performed in populations at risk [9, 10]. Another important diagnostic issue concerns the potential role for other noninvasive imaging modalities in diagnosing HFpEF. From a therapeutic standpoint the question remains unanswered — which pathophysiological pathways should be modified in order to slow down or to stop the disease. Is there one leading pathway eventually resulting in HFpEF, or is it a mixture of interacting mechanisms?

Heart failure with preserved ejection fraction of the left ventricle became a dominant form of HF worldwide and is associated with high morbidity and mortality. Despite enormous scientific effort there are still many clinical doubts regarding this clinical syndrome. Therefore, one has to appreciate an excellent review on this topic prepared by Club 30 of the Polish Cardiac Society published in current issue of "Cardiology Journal" [11]. Indeed, a guide to the guidelines is still needed while dealing with HFpEF and its dilemmas.

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Cardiac injury is independently associated with mortality irrespective of comorbidity in hospitalized patients with coronavirus disease 2019

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Article p. 489

Coronavirus disease 2019 (COVID-19) has become a global pandemic and an unexpected public health crisis [1]. Although respiratory symptoms are common clinical manifestations of COVID-19, some patients will experience cardiovascular (CV) complications [1, 2]. Many previous studies have been reported that pre-existing CV diseases (CVD) and in-hospital myocardial injury are both key determinants of COVID-19 mortality [2]. Moreover, COVID-19 related cardiac injury occurs more frequently in patents with pre-existing CV comorbidities [3]. However, whether the increased mortality in patients with cardiac injury can be attributed to a higher prevalence of comorbidities in COVID-19 patients remains unclear.

In this issue of "Cardiology Journal", Lorente-Ros et al. [4] described the associations between cardiac injury and mortality in COVID-19 patients, and whether this link was related to patient comorbidities. Between March 18 and March 23 in 2020, 707 consecutive adult patients admitted to a large tertiary hospital with confirmed COVID-19 were retrospectively included. The demographic data, medical history, laboratory results and clinical outcomes were gathered, and the Charlson comorbidity index (CCI) was calculated to quantify the degree of comorbidities. COVID-19 associated cardiac injury is defined if the level of serum cardiac troponin (cTn) I/T increase is above the 99th percentile upper reference limit after excluding obstructive coronary artery disease [2, 5]. The results showed that 20.9% of COVID-19 patients presented with cardiac injury [4]. This finding is similar with previous findings in Wuhan, China [6–8]. In the multivariate-adjusted Cox proportional hazard regression model, cTnI, age, C-reactive protein and creatinine on admission were independently associated with a higher risk of all-cause mortality within 30 days [4]. In a second Cox model, adjusted for CCI to account for age and comorbidity, cTnI was also proved as the independent indicator associated with higher risk of mortality (hazard ratio 2.31, 95% confidence interval 1.57–3.39, $p < 0.001$) in COVID-19 [4]. Thus, cardiac injury is independently associated with mortality irrespective of baseline comorbidities. And the addition of cTnI to multivariate regression models significantly improves their performance in predicting mortality in a time-dependent receiver operating characteristic curve [4].

In another study, Cao et al. [9] included 244 COVID-19 patients with no pre-existing CVD, and revealed that 11% of these patients had increased cTnI levels (> 40 ng/L) on admission. And serum cTnI levels provided independent prediction to both disease severity and 30-day in-hospital mortality in these COVID-19 patients with no prior

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CVD [9]. It further indicated that myocardial injury is an independent predictor for mortality irrespective of CV comorbidities in COVID-19.

Based on the predictive value of troponin to mortality, the determination of cardiac injury biomarkers on admission and its combination with CCI can classify patients into three risk groups (high, intermediate and low), which may shed important light on the clinical management of COVID-19. The elevation of troponin may be interpreted as an early warning sign with aggravating the disease, identifying those patients who might require careful monitoring. Not only that, aggressive cardioprotective treatments could be applied to COVID-19 patients with cardiac injury in a timely manner.

Circulating cardiac troponin is a marker of cardiac injury, including but not limited to myocarditis or myocardial infarction. Potential mechanisms of myocardial injury in COVID-19 include viral myocarditis induced by virus infection and autoimmune response, coronary microvascular ischemia mediated by endothelia cell dysfunction, stress cardiomyopathy and tachyarrhythmia attributable to adrenergic stimulation, atherothrombosis triggered by the proinflammatory and prothrombotic state, and myocardial oxygen supply or demand imbalance with hypoxia, hypotension, or tachycardia [10]. Thus, myocardial injury can occur independently or on the basis of comorbidity in COVID-19.

Treatments for myocardial injury in COVID-19 mainly refer to anti-viral therapy and anti-inflammatory therapy. Since the outbreak of COVID-19, a few anti-virus agents have been proposed. Among them, the most hopeful one is remdesivir. In the randomized controlled trial (RCT) of COVID-19, remdesivir did not show obvious clinical benefit for severe COVID-19 patients [11]. Although no antiviral drugs have been proved to be effective by RCT, several drugs may have certain therapeutic effects after clinical observation. In the Chinese management guidelines for COVID-19, interferon-α, ribavirin, chloroquine phosphate and abidol could be recommended [12]. For anti-inflammatory drugs, corticosteroid could be the first one shown to reduce the mortality of COVID-19 patients [2]. Also in the Chinese management guideline for COVID-19, patients with progressive hypoxia, rapid progress in lung imaging, and excessive inflammatory response are advised to use glucocorticoid within a short time [12]. The other anti-inflammatory or immunomodulation therapies such as intravenous immunoglobulin, anti-interleukin-6 receptor monoclonal antibody, convalescent plasma, blood purification, mesenchymal stem cell infusion, among others have also proved to be effective in a portion of COVID-19 patients [12]. For severe and critical COVID-19 patients with cardiac injury, it is necessary to carry out respiratory and circulatory support treatment such as mechanical ventilation, continuous renal replacement therapy, and extracorporeal membrane oxygenation.

COVID-19 patients with pre-existing medical conditions are susceptible to cardiac injury. However, myocardial injury is an independent predictor for mortality, irrespective of comorbidity in COVID-19. The management of myocardial injury in COVID-19 is of great importance and should be continuously improved in future research.

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"The significant other": Evaluation of side branch ostial compromise in bifurcation stenting

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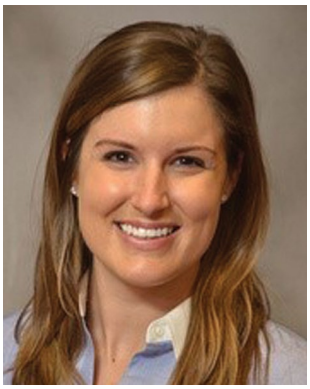

Article p. 507

"Everything is nothing with a twist"
Kurt Vonnegut

Background

The overall numbers of percutaneous coronary interventions of bifurcation lesions continue to increase worldwide. Interventions however, remain challenging. Despite an increasing anatomical and physiological understanding of the dividing coronary tree and a fast-growing refinement of stenting techniques for bifurcation lesions, there remains a risk of side branch (SB) ostial compromise or in the worst-case scenario, SB closure during stent implantation [1]. Evaluating the risk of SB compromise or closure during bifurcation stenting is one of the major considerations when planning the procedure. Furthermore, deciding which coronary bifurcation lesions that require an elective two-stent procedure, because of the risk of SB closure, remains a fundamental controversy worldwide [2]. The European Bifurcation Club recommends a provisional stenting approach to most bifurcation lesions, the philosophy is to keep the procedure as simple as possible (but not simpler). It is recommended that the operator use two wires (with the SB wire, as protection for potential rescue procedures should the SB close). The procedure can then develop from one initial stent in the main branch (MB) across the SB. The stent is recommended to be implanted with respect to the distal diameter of the MB. According to the philosophy of provisional step-wise bifurcation stenting, the implantation of the initial stent is finalized by the proximal optimization technique to correct the proximal stent malapposition and to open stent struts towards the SB. Thereafter the SB is only treated (by balloon dilatation, kissing balloon dilatation or stenting) if needed [2, 3]. By using this approach, it is possible to reduce number of stents needed and layers of metal composites in the coronary vessels, minimizing long-term risks and optimizing angiographic outcomes and the procedure is also cost-effective [4].

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Evaluation of whether or not to leave the SB without intervention when the SB ostium is impaired after MB stent implantation is a crucial step in the provisional approach. The angiographic evaluation (quantitative coronary assessment [QCA], eye balling) is difficult and can be misleading. Fractional flow reserve (FFR) evaluation carries a risk of compromising the SB by dissection during rewiring and FFR evaluations in bifurcations, which can be misleading because of signal crosstalk [4]. Accordingly, a deeper anatomical and physiological understanding of the stent — vessel wall interaction and its role in SB ostial compromise during stent implantation is needed.

A novel mathematical approach to understanding SB compromise in bifurcation stenting

In this issue of 'Cardiology Journal', Vasilev et al. [5] present an excellent mathematical model and validation to understand the mechanism of SB compromise after MB stenting. The authors took an elegant approach to demonstrate that there is a severe overestimation of stenosis severity when the areas are estimated to be circular (mathematically) instead of an oval. This provides novel insight into the evaluation of SB compromise after stenting the MB across the SB. By bringing the clinical observations of the SB ostium from three-dimensional fluoroscopy reconstructions the authors quantitatively replicated the natural physiology and describe the flow reduction over the compromised SB ostium. These precise measurements described and calculated comparison highlights the multifactorial elements in SB compromise during stenting, and thereby increases the understanding of the final interaction between the stented segment and the paired anatomic and physiological system.

The model was accomplished through utilizing patient QCA analyses data from a clinical trial to test the hypothesis that accounting for the elliptical SB anatomy would elucidate the most accurate prediction of stenting strategy. FFR data was collected and mathematically determined the square area of the SB before and after stenting. Subsequently, three quantitative approaches were utilized to determine the most accurately representative approach in calculating the cross-sectional area.

The authors took significant quantitative considerations; it was accurately pointed out that previous works considered the primary equation to identify the ostial dimensions transcendental functions. However, the function described in these previous works do not satisfy the polynomial equation [6]. Uniquely, the authors have circumnavigated these pitfalls in detail, the basics of the assumptions were: 1) Circular SB ostium shape after main vessel (MV) stenting was in a standard estimate of SB ostial stenosis; 2) Elliptical ostium shape at SB assumed after MV stenting accounting for SB reference diameter, taking into account for long axis ellipse; 3) Elliptical ostium shape at SB assumed after MV stenting, calculated with minimal lumen diameter at SB ostium before stenting, considered for long axis ellipse calculation (Fig. 1) From this validation set, the authors concluded that the stenosis area was significantly larger when utilizing the circular formula when compared to the elliptical formula demonstrating a value of considering the mathematics in clinical decision-making (Fig. 1).

A consequence of solving for the elliptical area inadvertently sheds light on the quantitative effect of over dilation of the distal SB. Although the authors main focus was to better understand SB compromise and a true reflection of the ostial area, solving for this utilizing the clinical QCA data describes the close approximation from the Ramunjun formula. Thus, optimizing many of these parameters is highly important to transform the clinical observations into something that is possible to computationally simulate [7, 8].

Translating the quantitative approach to SB ostial impairment into clinical practice

The cause of SB compromise during stenting of the MV has been attributed to as well, plaque shift from the MV into the SB as to carina shift due to pushing of the carina tip into the ostium of the SB during stent implantation. The coronary arteries divide in a fractal manner and the diameter of the branches correlate to the physical principle of minimal workload [9]. Because of these underlying biological principles, the coronary vessels taper (Fig. 1). This phenomenon is most prevalent after takeoff of a SB resulting in discrepancy in vessel diameter between the proximal vessel and the distal vessels in a bifurcation. If a tubular stent is implanted across the SB and implanted with respect to the proximal diameter of the MB it will be overdilated in the distal MB, thereby increasing the risk of SB ostial compromise. The vessel will be overstretched in the area immediately below the takeoff of the SB, increasing the risk for an overstretched oval deformation and consequently

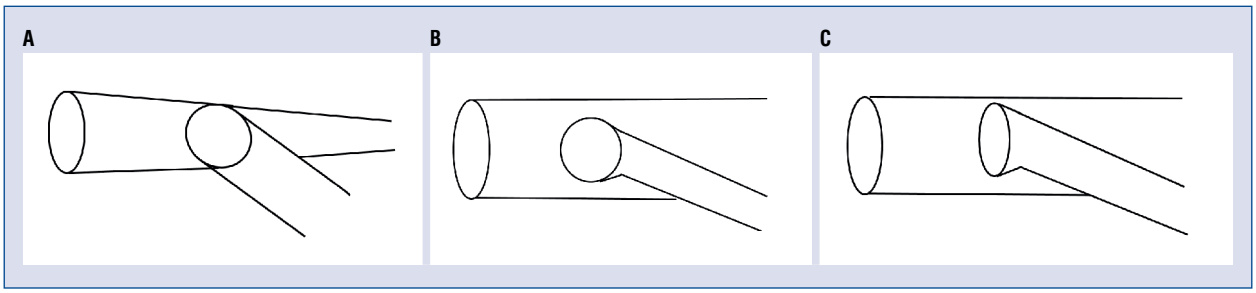

Figure 1. Quantification of ostial shift and effect on side branch (SB) shape by distal main branch (MB) over dilation. **A.** Tapered nature of MB. The formula Ac = π.ds^2/4 assumes the SB is circular and ds is the reference SB; **B.** Main branch after stenting with stent dilatation according to the proximal MB diameter. The SB diameter, ds, was taken as a reference in those calculations. The respective area stenosis (AS) was calculated as ASds = (1–Ae1/Asb) × 100, where ASds is ostial elliptic AS of the SB, Ae1 — SB calculated ostial area, Asb — reference SB vessel area (calculated based on vessel diameter 1 mm distal from the end of visually diseased end of plaque segment); **C.** Main branch after stenting with stent dilatation according to the proximal MB diameter, taking into account the overstretching of the distal part of the vessel, with oval transformation of the SB ostium. For the third calculation of SB ostial area after stenting, the same assumptions and formulas were used as in the second, but as a reference diameter instead of SB reference diameter the SB ostial minimal lumen diameter before stenting was used (i.e. this is the minimal lumen diameter before stenting, as measured from quantitative coronary assessment). The corresponding AS was labeled ASmld = (1–Ae2/Asb) × 100, where ASmld is ostial AS (in percentages), Ae2 — ostial SB area calculated according to the above assumptions, Asb — as above.

introducing the "nipping" appearance of the SB ostium, as seen on the angiograms (Fig. 1). It seems most likely that ostial compromise is due to mechanistic overstretching of the vessel by the stent implantation that will bring the circular ostium to an oval form. Plaque shift due to the reorganizations of the soft plaque by the pressure applied during stent implantation as well as the carina shift, partly due to overstretching and partly due to to pushing the carina toward the SB, which are likely to add to ostial compromise.

Vasilev et al. [5] shall be congratulated for bringing the SB ostial compromise attributed to distal vessel overstretching, during stent implantation into mathematical formulas. This achievement has clarified the mechanism behind the clinical optical coherence tomography observation of elliptical stretch and deformation of the SB ostium and increased understanding of SB ostial compromise. Furthermore, the formulas have founded the base for realistic calculations of cross-sectional area of the compromised SB ostium and thereby made it possible to evaluate the resulting FFR by simulation and explain the observed deviations from the actual measured FFR values calculated with the assumption of a circular SB ostium. In conclusion, mathematical modeling has increased the understanding of device and vessel wall interaction and made the simulation of the consequences of SB compromise possible.

Future applications for mathematical modeling in bifurcation stenting

There are distinct advantages to leveraging mathematical models over computational fluid dynamics and other computational tools in certain aspects of clinical research. In this example, quantitative analysis was beneficial and acted as a powerful tool that both validates the peri-procedural work, provides evidence for our intuition and guides in clinical decision-making. In the future, this mathematical analysis may merge with fluid dynamics and other computational tools in order broaden the whole picture, merging multi-physics models, that couple contraction, electrophysiology and flow with a quantitative analysis within the procedure [7–9]. Therefore, mathematical modeling can be a cornerstone for translating biological observations into formulas that can be validated by simulation and broaden our view and understanding of device vessel wall interaction during stent implantation.

In an overall conclusion, numerical analysis, mathematical modeling and computational simulation has the potential to be the tool of choice in the evaluation of various technical issues and their relation to function and outcome in bifurcation stenting. The advancement of supercomputers can maximize the output and improve simulation by expansion. By including boundary conditions and

flow parameters that are more precise and based on mathematic modeling as part of the models, the possibility to test and simulate anatomy that is more realistic and physical conditions are widely open. By following this path, the future is open to integrate anatomy, physiology and device interactions in the simulations to finally mimic the laws of nature and improve stent implantation in coronary bifurcation lesions.

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Myocardial infarction in the shadow of COVID-19

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Myocardial infarction (MI), the top cause of death globally, is associated with a high risk of heart failure development. The prognosis of MI depends on the ischemia size, which is correlated with the time from the onset of symptoms to reperfusion. Percutaneous coronary intervention (PCI) is a well-established treatment option for patients with MI [1]. In recent years, the most significant emphasis has been placed on the development of cardiology hubs of local networks that provide the shortest time to revascularization and improvement of MI treatment outcomes [2]. Moreover, managed care after MI has significantly improved results by increasing rates of cardiac recovery, complete revascularization, or implantation of an implantable cardioverter-defibrillator [3]. This situation has changed dramatically since the beginning of the pandemic of coronavirus disease (COVID-19), where over a very short period of time, an increased number of infected people were seeking medical assistance. COVID-19 confers the risk of severe acute respiratory syndrome caused by severe respiratory tract infection. Since the beginning of the pandemic, health systems have struggled to reorganize their health priorities due to the overwhelming number of patients requiring assistance and limited medical equipment. Emergency departments were transformed to be specifically dedicated to COVID-19 management. Many governmental authorities recommended the use of social distancing and 'stay at home and away from others,' as a means to control the spread of these infections and to be able to provide medical equipment and staff to treat those patients already hospitalized. While MI networks were and can presently still provide care for patients with MI, this care now involves another layer of caution. COVID-19 has changed the nature of medical consultations after MI, emphasizing virtual consulting with patients. The first patients of COVID-19 were reported in December of 2019 in Wuhan, China, and rapidly spread to the rest of the world [4, 5]. In Europe, northern Italy was the first affected region with the highest total case count and an exponential increase in the number of cases. What was observed in the MI care networks, was that many patients with the acute coronary syndrome (ACS) refrained from obtaining emergency medical services for fear of acquiring COVID-19 infection in the hospitals overwhelmed with COVID-19 patients. This dramatic situation was reported all over the world as catheterization laboratories noted a dramatic reduction of ACS patients and an increase in mortality, which could not be solely explained by complications caused by COVID-19. Specifically, data from northern Italy showed a drastic reduction in the number of ACS patients reporting to cardiovascular centers at the time of the COVID-19 outbreak [6]. A comparable situation was observed in the United States of America, where during the early phase of the COVID-19 pandemic, the reduction of PCI in ST-segment elevation myocardial infarction (STEMI) patients was 38% [7]. The data from Spain was also alarming, which showed a 40% decrease in the number of PCI in STEMI patients [8], while in Switzerland, STEMI referrals decreased by 56% [9]. Data from Poland [10, 11] showed a greater decline in the number of procedures for non-STEMI (NSTEMI), unstable angina or chronic coronary syndrome than in those for STEMI. Legutko et al. [10] reported that after lockdown the number of PCI in STEMI decreased by 19.2%, while in a later period it declined by 16.2%. Conversely, the decrease of PCI procedures in NSTEMI after lockdown was more pronounced and reached 33.5%, while later on it even reached 36.1%. However, Siudak et al. [11] noted that in comparison to the corresponding period of the previous year there was a reduction in PCI of 36% for STEMI and 39% for NSTEMI. The statistics from other countries would presumably demonstrate similar trends; however, more data in this field has not yet been published. The data revealed that patients with ACS requiring PCI had been undertreated. A natural consequence of this situation is the growth in MI complications, translating into increased morbidity and mortality. Thus, this aspect of care for cardiac patients requires urgent attention. In addition to all the information relayed to the general public about the COVID-19 pandemic, the need for immediate contact with emergency medical services in case of chest pain should be emphasized. Hospitals should continue to use COVID-19 protocol, but healthcare professionals should continuously be aware of the fact that ACSs still represent the leading cause of death in a broad population despite current epidemiologic status. Although ACS may be accompanied by active COVID-19 infection, or even worse [12], COVID-19-associated myocarditis may mimic ACS [13], the need for urgent invasive coronary angiography in ST-segment elevation ACS is still of vital importance and should not be neglected [12]. This does not prevent the need for caution of infection, and presumably, each patient with ACS

should be regarded as COVID-19 positive until a negative test result is obtained. Nasopharyngeal swab for COVID-19 infection should be acquired in all patients upon admission, while all medical staff should be provided with adequate personal protection equipment against COVID-19. This was recently stressed in a consensus document by the European Association of Percutaneous Coronary Interventions (EAPCI) [14]. Only in this way can we improve the treatment outcomes of patients with ACS during a pandemic period. Let us not waste the decades of progress in the field of invasive MI treatment!

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COVID-19 and its implication for venous thromboembolism

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COVID-19 and its implication for venous thromboembolism

Coronavirus disease (COVID-19) is caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is responsible for the ongoing 2019–2020 pandemic. Infected patients can be asymptomatic or show a range of symptoms including: fever, cough, fatigue, and dyspnea. These symptoms, except fever, are also typical for acute pulmonary embolism (APE). The overlapping symptoms of this diseases may result in under-recognition of APE.

Patients with COVID-19 infections are at an increased risk of thromboembolic complications. In hospitalized patients, a sudden deterioration of crucial vital parameters including tachycardia, hypotension, desaturation should suggest APE. Of note, temporary SIQIIITIII pattern in electrocardiogram, similar to alterations observed in APE was reported in COVID-19 patients [1].

Incidence of venous thromboembolism in patients with COVID-19

There is an increasing number of reports on thromboembolic complications in COVID-19 patients. Klok et al. [2] analyzed data of 184 patients (mean age 64 ± 12 years, 24% female) admitted to the intensive care unit (ICU) of Dutch hospitals due to proven COVID-19 pneumonia. All patients received at least prophylactic doses of nadroparin. The composite outcome was symptomatic APE, deep-vein thrombosis, ischemic stroke, myocardial infarction, or systemic arterial embolism. The cumulative incidence of the composite outcome was 31% (95% confidence interval [CI] 20–41%), of which computed tomography pulmonary angiogram and/or ultrasonography confirmed venous thromboembolism (VTE) in 27% (95% CI 17–37%) and arterial thrombotic events in 3.7% (95% CI 0–8.2%). APE was the most frequent thrombotic complication (n = 25, 81%) [2].

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Interesting data come from Wuhan, China, published by Cui et al. [3], 81 patients (mean age 59.9 ± 14.1 years, 54% female) with severe coronavirus pneumonia were enrolled. The incidence of VTE in these patients was 25% (20/81), of which 8 patients with VTE events died [3]. Wichmann et al. [4] performed complete autopsies of the 12 consecutive COVID-19 positive deaths. Autopsy revealed deep venous thrombosis in 7 of 12 patients (58%) in whom VTE was not suspected before death. APE was the direct cause of death in 4 patients [4].

In a recently published, prospective study, Helms et al. [5] described the COVID-19 induced thrombotic complications in 150 consecutive COVID-19 acute respiratory distress syndrome patients. Despite anticoagulation 64 clinically relevant thrombotic complications were mainly diagnosed as APE (16.7%) [5].

There is also interesting data from Lombardy, an Italian region that was most affected by the pandemic. In one paper, all cases of COVID-19 in-hospital patients undergoing duplex ultrasound for clinically suspected deep vein thrombosis. Of 101 duplex ultrasounds performed, 42 were positive for deep vein thrombosis. Moreover, in 24 patients APE was diagnosed. Three patients in ICU were already under anticoagulant therapy, while the rest were receiving prophylactic dosages of low molecular weight heparins [6].

The available data support the high incidence of thromboembolic complications in COVID-19 patients despite thromboembolism prophylaxis.

Potential mechanisms of increased VTE risk in COVID-19 patients

Several mechanisms in patients with COVID-19 potentially promote the development of VTE. They fulfil at least two of the three criteria of Virchow's triad: reduced venous flow from immobility, as well as prothrombotic changes due to inflammatory state [7]. Vessel wall changes, the third criteria of Virchow's triad, may also be present in infected patients Moreover, hypoxia in COVID-19 pneumonia subjects may also be a factor for increasing the risk of thromboembolic complications.

Serum level of angiotensin 2 is significantly elevated in infected patients, activating the renin––angiotensin system, which can cause widespread endothelial dysfunction. It is worth noting that the virus can bind to the endothelial cells via angiotensin 2 receptors — which are present mainly in the lungs, heart, and kidneys, followed by endothelial cells. This process may finally damage blood vessels and increase the risk of thrombosis [8]. It is also possible that antiphospholipid antibodies, that appear transiently in critically ill patients, may cause an increased risk of thromboembolism. There is a case report of 3 critically ill patients with confirmed COVID-19. They presented clinically significant ischemia of the lower limbs and multiple cerebral infarcts. Among these patients, antiphospholipid antibodies were detected [9].

Laboratory findings and diagnostic approach in patients with COVID-19

In COVID-19 patients the most typical laboratory findings include leukopenia, lymphocytopenia, mild thrombocytopenia, prolonged prothrombin time, increased D-dimer levels, and high fibrinogen level at the beginning of the disease followed by low fibrinogen levels in severe cases [4, 10, 11]. Increased values of D-dimer may be secondary to an infection and inflammation. Therefore, in COVID-19 patients, the specificity of D-dimer tests in diagnostics of VTE is lesser than in a healthy population. Disseminated intravascular coagulopathy is present in severe cases of SARS-CoV-2. It is recommended only to order diagnostic tests for pulmonary embolism when it is clinically suspected, however pulmonary embolism should be considered in differential diagnosis. Even if the specificity of D-dimer tests may be lower, it is still worthwhile following diagnostic algorithms starting with pre-test probability and D-dimer testing. This may reduce the number of necessary computed tomography-scan examinations with associated complications, as well as the associated deployment of resources and personnel for transporting a patient for a computed tomography scan with isolation precautions. Multidetector computed tomographic pulmonary angiography is the method of choice for imaging pulmonary vasculature in patients with suspected APE. In hemodynamically unstable patients, transthoracic echocardiography may be a first line examination. Right ventricular overload and dysfunction might be sufficient to prompt immediate reperfusion without further testing [12].

Lower limb compression ultrasonography may be useful in COVID-19 patients. Compression ultrasonography has a sensitivity > 90% and specificity > 95% for proximal symptomatic deep vein thrombosis. Compression ultrasonography should be a part of point of care ultrasound particularly in patients with unexplained right ventricular dysfunction, unexplained hypoxemia or in patients

with suspected APE who are unable undergo further evaluation.

Every single physical examination, laboratory test, or imaging of the patients including computed tomographic pulmonary angiography, compression ultrasonography, and echocardiography, requires the full protection of staff. Additionally, all equipment should be sterilized.

According to the literature, an increase of D-dimer level correlates with an increase in hospital mortality. Tang et al. [11] revealed data of 183 consecutive patients with confirmed coronavirus pneumonia. The overall mortality was 11.5%. The non-survivors revealed significantly higher D-dimer levels compared to survivors (2.12 [0.77–5.27] vs. 0.61 [0.35–1.29] μg/mL, $p < 0.001$) [11].

Recently, Figliozzi et al. [13] published a metanalysis included 49 studies and a total of 20,211 patients. An increased D-dimer level was related to adverse combined outcome (death, severe presentation, hospitalization in ICU and/or mechanical ventilation (odds ratio [OR] 4.39, 1.85–10.41, $p = 0.003$) and death (OR 4.40, 1.10–17.58, $p = 0.04$) [13].

Treatment of VTE patients

According to the European Society of Cardiology (ESC) guidelines, initiation of anticoagulation is recommended without delay in patients with high or intermediate clinical probability of APE, while diagnostic workup is in process [12]. It is very important in COVID-19 patients among whom most have a high or intermediate clinical probability of VTE. Treatment of VTE should be conducted in accordance with the ESC guidelines on the basis of risk assessment. Hemodynamically unstable, high-risk patients, should undergo immediate reperfusion by thrombolysis. It should be noted that many of the patients with COVID-19 have an absolute or a relative contraindication to thrombolysis such as thrombocytopenia, disseminated intravascular coagulation or a recent invasive procedure. Percutaneous catheter direct treatment should be considered for patients with high-risk APE, in whom thrombolysis is contraindicated or failed or for intermediate high risk with hemodynamic deterioration on anticoagulation treatment [8].

The anticoagulation therapy for stable APE patients is usually low molecular weight heparin (LMWH) or direct oral anticoagulants (DOAC). Unfractionated heparin may be initially preferred in intermediate-high risk patients and in subjects with severe renal failure or extreme obesity. After initial heparin treatment in stable APE patients, DOAC is preferred. However, drug interactions between DOAC and medical treatment of COVID-19 should be considered. Lopinavir/ritonavir inhibit cytochrome P450 3A4 and thus may increase the activity of NOAC — and therefore, the risk of bleeding. It should be emphasized that vitamin K antagonists are not recommended, except for patients with mechanical valves or antiphospholipid syndrome [14].

Thromboprophylaxis

Due to the increased risk of thromboembolic complications in patients with COVID-19, International Society on Thrombosis and Hemostasis (ISTH) and American Society of Hematology (ASH) guidelines advise prophylactic LMWH in all hospitalized COVID-19 patients in the absence of any contraindications [15, 16]. Therefore, thromboprophylaxis should be considered in all hospitalized patients due to COVID-19. Some authors recommended considering higher prophylactic doses of anticoagulation such as enoxaparin 0.5 mg/kg b.i.d. or 1 mg/kg once daily [2, 7]. Similar, according to CHEST Guideline and Expert Panel Report all hospitalized patients with COVID-19 are at increased risk of VTE. Therefore experts suggest against individualized VTE risk assessment and suggest anticoagulant thromboprophylaxis in all hospitalized patients with COVID-19 in the absence of contraindication [17]. Only a few papers address the issue of extended duration prophylaxis. Post discharge VTE and major bleeding rates in COVID-19 patients are currently unknown. Most experts recommended against routine extended, post discharge, duration prophylaxis in hospitalized patients, although an individualized approach for each patient should be considered [17].

Conclusions

Patients with COVID-19 infections are at increased risk of thromboembolic complications, a potentially preventable cause of death. Hospitalized patients should receive VTE prophylaxis. The diagnostic approach should be carried out according to the ESC guidelines, but physicians must be aware of the lower specificity of the D-dimer test. Every single physical examination, laboratory test, and imaging requires the full protection of staff. The anticoagulation therapy for stable VTE patients is usually LMWH or DOAC; vitamin K antagonists are **not recommended**.

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Impaired microcirculation function in COVID-19 and implications for potential therapies

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), responsible for the coronavirus disease 2019 (COVID-19), is a new ribonucleic acid virus strain from the Coronaviridae family [1]. From December 2019 to June 2020, the COVID-19 pandemic included over 7.6 million confirmed cases in 216 countries, and over 427,000 deaths [2]. Acute respiratory distress syndrome (ARDS) is one of the most severe complications of COVID-19 [3]. Based on autopsy studies, the ARDS associated with COVID-19 has distinct features — lung damage is consistent with complement-mediated microvascular injury consisting of diffuse microthrombosis and hemorrhage, whereas the hallmarks of classic ARDS with alveolar damage and hyaline membranes are not prominent [4]. Microvascular injury is typically not accompanied by gross pulmonary thromboembolism and parenchymal inflammation [5]. In addition, acro-ischemia including finger/toe cyanosis, skin bullae and dry gangrene were prodromal or early symptoms of COVID-19 [6, 7], confirming skin damage patterns consistent with microvascular thrombosis. In fact, the cutaneous manifestations are present in up to 20% of patients with COVID-19 and has been classified into five clinical patterns, with pseudo-chilblain being the most, and livedo or necrosis — the least frequent [8]. Thus, microvascular thrombosis seems to be one of the main pathological findings in COVID-19 patients [9, 10].

In addition to respiratory disease, cardiovascular complications are rapidly emerging as a key threat in COVID-19 [11]. In a recent meta-analysis of 8 studies from China including 46,248 infected patients, 7% of patients experienced myocardial injury (22% of these were critically ill), as evidenced by elevated cardiac troponin [12]. Noteworthy, patients with myocardial injury had higher in-hospital mortality (37.5%) than patients with cardiovascular disease (CVD) but without myocardial injury (13.3%), or patients without CVD (7.6%). Moreover, if myocardial injury was present in patients with preexisting CVD, the mortality increased even more (69.4%) [13]. Clearly,

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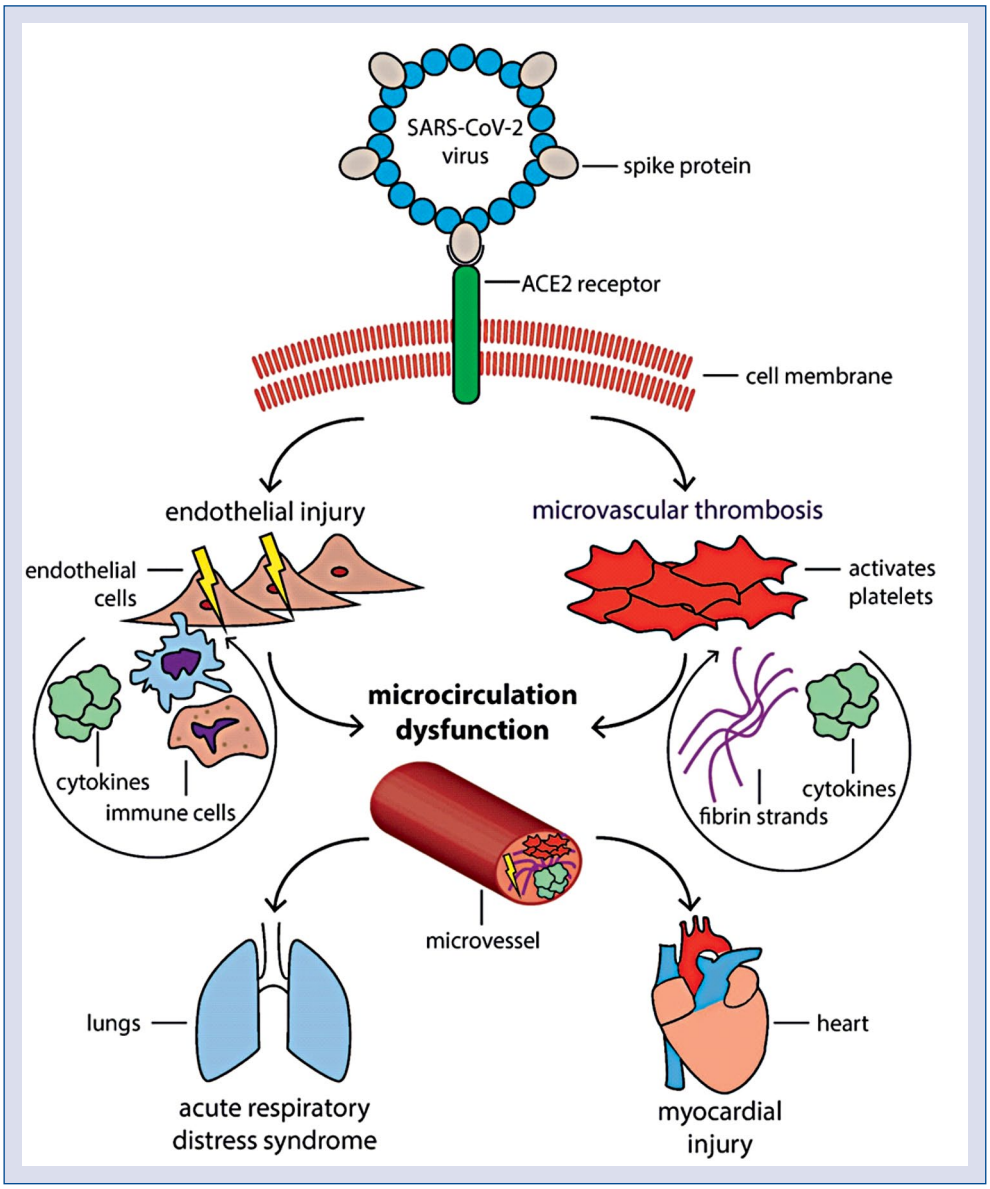

Figure 1. Pathophysiological mechanisms underlying the most severe complications associated with COVID-19, including acute respiratory distress syndrome and myocardial injury; SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2; ACE2 — angiotensin-converting enzyme 2.

myocardial injury and underlying CVD markedly deteriorates the prognosis in COVID-19 [14]. The possible mechanisms explaining this association include (i) cytokine storm, (ii) microangiopathy, (iii) viral myocarditis, (iv) stress-induced cardiomyopathy, (iv) classic myocardial infarction due to infection-induced atherosclerotic plaque instability [15, 16]. All these mechanisms have a common denominator, which is endothelial injury [17, 18].

SARS-CoV-2 enters target cells through angiotensin-converting enzyme (ACE) two receptors, which are especially widely expressed on the surface of lung epithelial cells and vascular endothelial cells in multiple organs [19, 20]. The viral infection of the endothelial cells leads to endothelial cell inflammation (endotheliitis). This triggers the immune responses responsible for a massive local release of pro-inflammatory cytokines and further aggravation of endothelial injury [21]. Since endothelium is indispensable for the maintenance of vascular homeostasis, endothelial dysfunction leads to vasoconstriction with subsequent organ ischemia and a procoagulant state. According to the previously mentioned meta-analysis, the most

prevalent comorbidities in the infected patients were those associated with preexisting endothelial dysfunction, including arterial hypertension (17 ± 7%) and diabetes mellitus (8 ± 6%), followed by coronary heart disease (5 ± 4%) [12], explaining why these patients have a predisposition to COVID-19 and worse prognosis associated with the infection [22].

Figure 1 summarizes the pathophysiological mechanisms underlying the most severe complications associated with COVID-19. Altogether, microvascular thrombosis and endotheliitis lead to impaired microcirculatory function in different vascular beds, which leads to COVID-19 related complications, including ARDS and myocardial injury. If so, therapies to improve microcirculatory function might prevent complications and subsequently improve prognosis. Established therapies to improve microcirculatory function, in patients with microvascular angina, for example, include ACE inhibitors and statins [23]. However, at this time, nearly all major societies do not recommend adding or stopping the angiotensin receptor enzyme inhibitors or other renin–angiotensin–aldosterone system antagonists in acute settings, unless done on clinical grounds independently of COVID-19, given the lack of evidence currently available on their potential benefit or harm [11]. Moreover, these therapies do not control anginal symptoms in up to 80% of patients with microvascular angina, urging the need for new treatment options [24].

The new treatment options to improve microcirculation function include ivabradine, nicorandil, ranolazine, or trimetazidine [23]. Ivabradine is a direct and selective inhibitor of the I(*f*) current in the sinus node, which reduces heart rate without affecting myocardial contractility and coronary vasomotor tone [25]. Nicorandil opens potassium channels and enhances nitric oxide production in vascular smooth muscle cells (VSMC), leading to vasodilation [26]. Ranolazine inhibits the late inward sodium channel and reduces calcium overload in cardiomyocytes, therefore improving left ventricular diastolic function and reducing the mechanical compression of microcirculation [26]. Finally, trimetazidine inhibits the reduction of adenosine triphosphate in cardiomyocytes, therefore shifting cardiac metabolism from fatty acid to glucose oxidation [27]. Out of the four novel anti-anginal agents, the combination of ranolazine and nicorandil seems to be especially promising in improving microcirculatory function due to the (i) complementary mechanisms of actions both at the cardiomyocyte and microcirculation VSMC level and (ii) promising preliminary results regarding improvement in microcirculatory function in patients with microvascular angina.

Interventional treatment of impaired microcirculatory function could be considered as an alternative to pharmacotherapy, especially for the highest risk patients, with myocardial injury and with pre-existing endothelial dysfunction. The coronary sinus Reducer is a new technology designed to reduce disabling symptoms and improve the quality of life of patients with chronic refractory angina. The Reducer is a transcatheter, a balloon-expandable metal mesh, designed to create a focal narrowing in the lumen of the coronary sinus to generate a pressure gradient across it, and thus to redistribute forces of blood flow from less ischemic to more ischemic subendocardium of the left ventricle. The procedure lasts about 20–30 min, and improved microcirculation function is achieved within 2 weeks following implantation, which is the time required for the device endothelization. In a systematic review of 6 clinical studies (n = 196), the Reducer device improved symptoms and objective indications of ischemia in 78.5% of patients [28]. In long-term follow-up of the first-in-man Reducer study (n = 14), no death or acute myocardial infarction and no device or procedure-related adverse events occurred up to 3 years following implantation [29]. Hence, implantation of the Reducer might essentially improve microcirculation function not only in patients with refractory angina but also in patients with impaired microcirculatory function in the course of COVID-19.

Altogether, we suggest that any strategy to improve microcirculatory function could prevent and/or attenuate the complications of COVID-19, especially those most severe, associated with the respiratory tract and cardiovascular system. Such strategies should be considered particularly for vulnerable patients with preexisting endothelial dysfunction, including smoking, hypertension, diabetes, and CVD, all of which are associated with adverse outcomes in COVID-19 [18, 30].

Conflict of interest: None declared

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Myocardial injury determination improves risk stratification and predicts mortality in COVID-19 patients

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Abstract

Background: *Despite being associated with worse prognosis in patients with COVID-19, systematic determination of myocardial injury is not recommended. The aim of the study was to study the effect of myocardial injury assessment on risk stratification of COVID-19 patients.*

Methods: *Seven hundred seven consecutive adult patients admitted to a large tertiary hospital with confirmed COVID-19 were included. Demographic data, comorbidities, laboratory results and clinical outcomes were recorded. Charlson comorbidity index (CCI) was calculated in order to quantify the degree of comorbidities. Independent association of cardiac troponin I (cTnI) increase with outcomes was evaluated by multivariate regression analyses and area under curve. In addition, propensity-score matching was performed to assemble a cohort of patients with similar baseline characteristics.*

Results: *In the matched cohort (mean age 66.76 ± 15.7 years, 37.3% females), cTnI increase above the upper limit was present in 20.9% of the population and was associated with worse clinical outcomes, including all-cause mortality within 30 days (45.1% vs. 23.2%; p = 0.005). The addition of cTnI to a multivariate prediction model showed a significant improvement in the area under the time-dependent receiver operating characteristic curve (0.775 vs. 0.756, ΔC-statistic = 0.019; 95% confidence interval 0.001–0.037). Use of renin–angiotensin–aldosterone system inhibitors was not associated with mortality after adjusting by baseline risk factors.*

Conclusions: *Myocardial injury is independently associated with adverse outcomes irrespective of baseline comorbidities and its addition to multivariate regression models significantly improves their performance in predicting mortality. The determination of myocardial injury biomarkers on hospital admission and its combination with CCI can classify patients in three risk groups (high, intermediate and low) with a clearly distinct 30-day mortality.* (Cardiol J 2020; 27, 5: 489–496)

Key words: cardiac injury, myocardial injury, troponin, coronavirus, COVID-19, cardiovascular disease

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Introduction

As of June 19, 2020, coronavirus disease 2019 (COVID-19) has affected more than 8 million people, causing more than 440,000 deaths worldwide [1]. To lessen the burden on health care systems and provide better care, prediction models that provide efficient diagnosis and prognosis of the disease are needed. Identifying people at high risk of experiencing worse outcomes might help the clinician in the routine decision-making process [2–4].

COVID-19 infection may have major repercussions for the cardiovascular system [5, 6]. Recent investigations suggest a high prevalence of myocardial injury in these patients that can be detected by an elevation of some cardiac biomarkers, such as cardiac troponins [2, 7, 8].

Myocardial injury defined as troponin elevation has been consistently associated with mortality in a variety of situations, including sepsis and pneumonia. The value of measuring troponins to better stratify patients and guide management has been suggested for COVID-19, but solid evidence is pending to support its incremental value and systematic evaluation. Many previous studies have been reported to be at high risk of bias [3]. Cardiovascular morbidity has also been associated with both worse outcomes in COVID-19. Whether the excess of mortality in patients with myocardial injury can be explained by the higher prevalence of comorbidities in this population is still a subject of discussion [4, 9–14].

The purpose of this study is to describe the association between troponin elevation and mortality and whether this link is irrespective of patient comorbidities, as well as to evaluate its incremental benefit as a risk stratification tool.

Methods

Study population

Between March 18, and March 23, 2020, consecutive patients aged 18 years and older admitted to a large tertiary hospital with COVID-19 infection were retrospectively included with prospective follow-up. Diagnosis of COVID-19 infection was established by positive test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral RNA in nasopharyngeal swab by real-time reverse-transcription polymerase chain reaction according to World Health Organization interim guidance [15]. The only exclusion criterion was primary cardiac presentation, i.e. type 1 myocardial infarction. This study was approved by the Local Ethics Committee and written informed consent was waived.

Patients were treated with lopinavir/ritonavir and hydroxychloroquine unless contraindicated. Antibiotics, glucocorticoid and other immunosuppressive agents (i.e. tocilizumab) were also used at physician discretion according to the in-hospital consensus protocol.

Data collection

Baseline data, including demographics, medical history and laboratory tests were collected from the local Electronic Medical Records. Previous concomitant conditions were carefully evaluated and age-adjusted Charlson comorbidity index (CCI; **Suppl. Table S1**) [16] was calculated in order to quantify the patient's degree of comorbidity. All patients were followed for 1 month. Time from symptoms to admission, length of hospital stays, illness severity, use of non-invasive ventilation, mechanical ventilation and all-cause mortality were recorded.

Development of acute respiratory distress syndrome (ARDS) according to the Berlin definition, with arterial partial pressure of oxygen (PaO_2) and fraction of inspired oxygen (FiO_2) ratio < 300 mmHg was used to identify severe manifestations of the disease. When PaO_2 was not available, peripheral capillary oxygen saturation (SpO_2) was used to estimate PaO_2 [17]. Acute kidney injury was identified according to the Kidney Disease: Improving Global Outcomes definition [18].

Laboratory procedures

An in-hospital protocol developed by the infectious diseases department was made available since the beginning of the local outbreak. Routine blood examination on admission with serum biochemical tests, cardiac troponin, complete blood count, coagulation profile and D-Dimer was part of this protocol. Abbott high-sensitivity cardiac troponin I (cTnI) was used for analysis of cTnI. Cut-off normal value was ≤ 14 ng/L.

During hospitalization, the timing, content and repetition of successive tests were indicated by the treating physicians. Peak values during hospitalization of creatinine, cTnI, hematocrit, D-Dimer, B-type natriuretic peptide and C-reactive protein (CRP) were recorded.

Ethical approval

Approval from the local ethics committee (*Comite etico de Investigacion clinica GAE Ramon y Cajal Area 4*) was granted as per local protocol.

Table 1. Baseline characteristics before and after propensity-score matching.

Characteristics	Before matching			After matching		
	Myocardial injury (n = 148)	No myocardial injury (n = 559)	Standardized differences, %	Myocardial injury (n = 112)	No myocardial injury (n = 112)	Standardized differences, %
Age [years]	78.7	63.4	114.0	76.3	75.5	6.1
Sex	48.0%	34.5%	27.5%	42.9%	43.8%	1.8%
Hypertension	76.4%	43.6%	70.1%	72.3%	77.7%	11.6%
Use of RAAS inhibitors	54.7%	25.8%	61.7%	50.0%	50.0%	0.0%
Diabetes (%)	24.3%	19.1%	12.6%	26.8%	23.2%	8.7%
Dyslipidemia	45.3%	31.1%	29.4%	44.6%	38.3%	13.0%
CKD	30.4%	6.08%	66.2%	17.9%	21.4%	9.7%
AF	25.0%	9.1%	43.1%	17.9%	22.3%	12.1%
IHD	15.5%	9.3%	19.0%	15.2%	11.6%	10.9%
HF history	32.4%	8.6%	61.6%	20.5%	22.3%	4.6%
Cerebrovascular disease	12.8%	4.1%	31.6%	8.0%	8.0%	0.0%
PAD	7.4%	2.1%	24.9%	3.6%	5.4%	8.4%
Cancer history	16.2%	9.8%	19.0%	17.0%	17.0%	0.0%
COPD	16.9%	7.5%	28.9%	14.3%	15.2%	2.7%
CCI (points)	6.5	3.2	115.1	5.4	5.4	0.6

AF — atrial fibrillation; CCI — Charlson comorbidity index; CKD — chronic kidney disease; COPD — chronic obstructive pulmonary disease; HF — heart failure; IHD — ischemic heart disease; PAD — peripheral artery disease; RAAS — renin–angiotensin–aldosterone system

Statistical analysis

Patients were divided in two groups: with and without myocardial injury on admission, defined as cTnI levels greater than the 99th percentile of a healthy population [19].

Multivariate Cox proportional hazards regression models were used to determine the association of cTnI with all-cause mortality within 30 days in hospitalized patients with COVID-19 disease (see **Supplementary material**: statistical analysis). Results were expressed as hazard ratios with 95% confidence intervals (CIs). Variables were selected a priori based on previous clinically related studies, clinical knowledge and practicality of measurement in acute medical emergencies. Variables were excluded if they had high multicollinearity. The number of predictors was restricted based on the total number of outcomes.

Kaplan-Meier survival curves were presented to compare survival in the groups of patients without myocardial injury versus those with myocardial injury. For analysing the interaction of comorbidities and cTnI, four groups were defined: no myocardial injury and CCI ≤ 4 (n = 411); no myocardial injury and CCI > 4 (n = 148); myocardial injury and CCI ≤ 4 (n = 46) and myocardial injury and CCI > 4 (n = 102). Time-dependent receiver-operator characteristic (ROC) curves were used to evaluate the incremental benefit of cTnI for predicting all-cause mortality. Areas under the ROC curves were calculated and compared. The integrated discrimination improvement index (IDI) and the continuous net reclassification improvement (cNRI) were also calculated.

Given the differences in the baseline characteristics between patients in the two groups (Table 1), a propensity score matching was performed using a multivariable logistic regression model with the use of myocardial injury as the dependent variable and all the baseline characteristics outlined in Table 1 as covariates. 1:1 matching was performed without replacement and with a calliper width equal to 0.2. Standardized differences were estimated before and after matching to assess balance. In the matched cohort, differences between groups were analysed with chi-squared test or sign test of matched pairs as appropriate.

Data were analysed using Stata 14.2 software (StataCorp LLC, Texas, United States) and R statistics version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria). For all the statistical analysis, a two-tailed p value of less than 0.05 was considered significant.

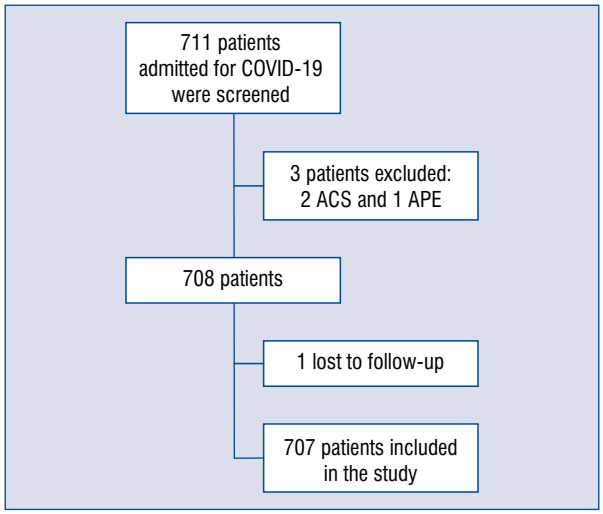

Figure 1. Patient selection. Flowchart showing the successive steps taken during the study; COVID-19 — coronavirus disease 2019; ACS — acute coronary syndrome; APE — acute pulmonary edema.

Results

Baseline characteristics

A total of 707 consecutive patients with confirmed COVID-19 were enrolled into the study (Fig. 1). Mean age was 66.6 ± 15.7 years and 37.3% were women. Prevalence of cardiovascular risk factors was high. The most common risk factor was hypertension (50.5%) followed by dyslipidemia (34.1%) and diabetes mellitus (20.2%). Chronic kidney disease was present in 11.2% of patients. Cancer history was also a relatively frequent condition, being present in almost 11.2% of patients. Median CCI was 3 (IQR 1 to 6).

There were significant differences in baseline characteristics between the two groups (Table 1). Patients with myocardial injury were older (78.7 vs. 63.4, $p < 0.001$) and were more frequently male (48.0% vs. 34.5%, $p = 0.003$). The burden of comorbidities was also higher in this group (median CCI of 6 vs. 3, $p < 0.001$).

A propensity-score matching was performed and 112 patients with myocardial injury on admission were matched with 112 patients without myocardial injury. After matching, an adequate comparability was shown by a decrease of the standardized differences to less than 20% for all covariates (Table 1).

Laboratory findings

Elevated cardiac troponin was patent in 20.9% of patients. The median level of cTnI on admission was 28.2 ± 15.7 ng/L) and mean peak level during hospitalization was 83.8 ± 68.7 ng/L. During hospitalization troponin levels increased in 57 (8.1%) of patients.

D-Dimer levels were elevated on admission in 70.6% of cases. Correlation between D-Dimer and peak troponin levels was weak (Spearman's ρ 0.24, $p < 0.001$).

Clinical outcomes

Of the 707 hospitalized patients, 368 (52.1%) had severe manifestation of COVID-19 defined by ARDS criteria, and 7.6% were admitted to the intensive care unit (ICU). Acute kidney injury (AKI) on admission was present in 9.6% of patients and 12.7% of cases developed AKI during hospitalization. Non-invasive mechanical ventilation was used in 6.5% of patients. After 1-month follow-up, 501 (70.9%) patients were discharged, 140 (19.8%) patients died and 66 (9.3%) patients remained hospitalized.

Median time-to-discharge was 9 days (IQR 5 to 14). The median time from initiation of symptoms to admission was 6 days (IQR 3 to 8), while the median time from onset of illness to death was days 14 days (IQR 9 to 19).

In the matched cohort all-cause mortality within 30 days was higher in those with cTnI elevation (41.1% vs. 23.2%; $p = 0.005$; Table 2). They also required more often non-invasive ventilation (15.2% vs. 5.4%, $p = 0.016$). However, there were no differences regarding ICU admission (6.3% vs. 4.5%, $p = 0.527$).

In the multivariate-adjusted Cox proportional hazard regression model, cTnI elevation was independently associated with a higher risk of all-cause mortality within 30 days. Age, CRP and creatinine on admission were also independent prognostic factors (Table 3). In a second Cox model, adjusted for CCI to account for age and comorbidity, cTnI elevation was also independently associated with higher risk of mortality (hazard ratio 2.31, 95% CI 1.57–3.39, $p < 0.001$).

Figure 2 shows Kaplan-Meier survival curves by myocardial injury groups (Fig. 2A) and by myocardial injury and CCI (Fig. 2B).

The addition of myocardial injury to the final multivariate clinical Cox model showed a significant improvement in the area under the ROC curve (0.77 vs. 0.79; Fig. 3). The C-statistic for the baseline clinical model was 0.756, while the addition of cTnI increased it to 0.775 (ΔC-statistic = 0.019; 95% CI 0.001–0.037). The cNRI was 35.2% (95% CI 0.4–45.5%, $p = 0.047$) while the IDI showed an incremental predictive ability ($p < 0.001$; Table 4).

Table 2. Outcomes and complications in the matched cohort.

	With myocardial injury (n = 112)	Without myocardial injury (n = 112)	P
ARDS	83 (74.1%)	65 (58.0%)	0.013
Non-invasive ventilation	17 (15.2%)	6 (5.4%)	0.016
ICU admission	7 (6.3%)	5 (4.5%)	0.527
Hospital stay, median days (IQR)	11 (6 to 17)	9 (5 to 13)	0.934
Mortality	46 (41.1%)	26 (23.2%)	0.005

ARDS — acute respiratory distress syndrome; ICU — intensive care unit; IQR — interquartile range

Table 3. Multivariate Cox regression analysis.

Predictors on admission	Univariable analysis; HR (95% CI)	P	Multivariable analysis; HR (95% CI)	P
Sex	1.108 (0.787–1.562)	0.556		
Age (per year)	1.080 (1.063–1.097)	< 0.001	1.069 (1.051–1.087)	< 0.001
Myocardial injury	4.355 (3.112–6.093)	< 0.001	1.716 (1.182–2.492)	0.005
Hypertension	1.960 (1.380–2.784)	< 0.001		
RAAS inhibitors use	1.700 (1.210–2.388)	0.002		
Hematocrit (per % decrease)	0.929 (0.905–0.954)	< 0.001		
Creatinine (per mg/dL)	1.469 (1.304–1.655)	< 0.001	1.291 (1.103–1.511)	< 0.001
D-Dimer (per ng/mL)	1.011 (0.986–1.036)	0.390		
C-reactive protein (per mg/L)	1.002 (1.002–1.003)	< 0.001	1.002 (1.001–1.003)	< 0.001
CCI (per point increase)	1.274 (1.216–1.335)	< 0.001		

CCI — Charlson comorbidity index; CI — confidence interval; HR — hazard ratio; RAAS — renin–angiotensin–aldosterone system

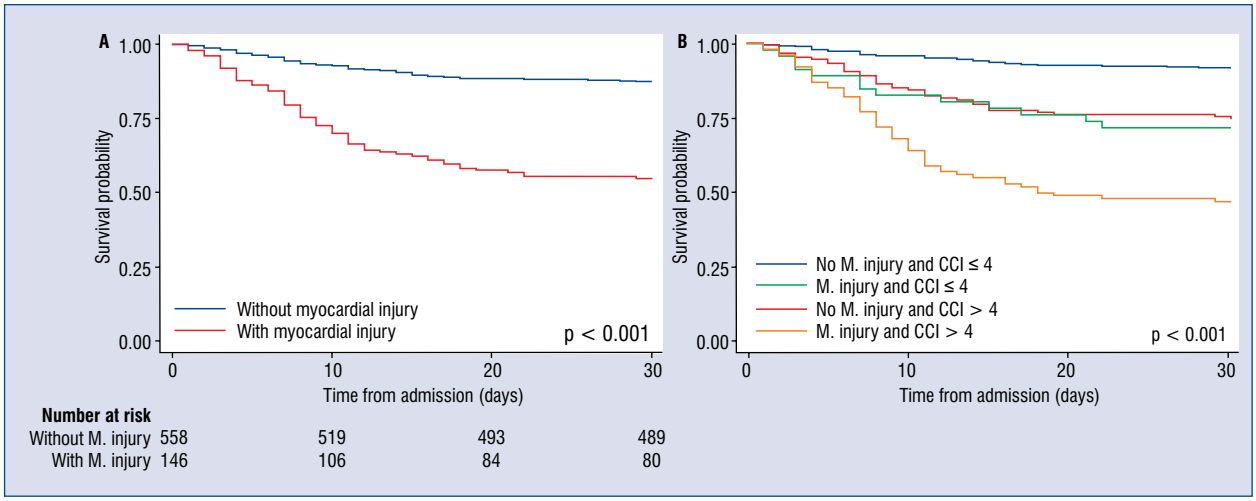

Figure 2. Event-free survival over time with the Kaplan-Meier method for myocardial injury (M. injury; **A**) and myocardial injury and Charlson comorbidity index (CCI; **B**).

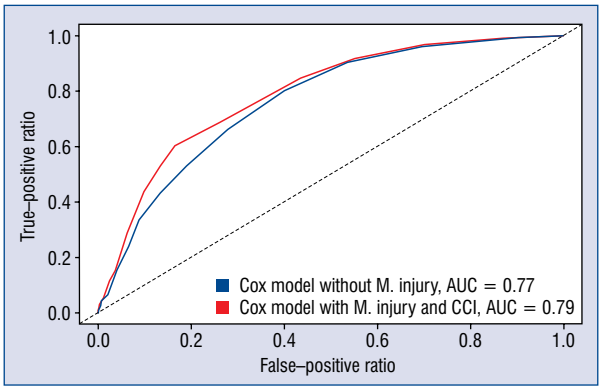

Figure 3. Receiver operating characteristic curves for the baseline Cox model (including Charlson comorbidity index [CCI]) in blue and for the multivariate model with the addition of myocardial injury in red; AUC — area under the curve; M. injury — myocardial injury.

Use of RAAS inhibitors

Although use of renin–angiotensin–aldosterone system (RAAS) inhibitors was more prevalent in patients who died (42.9% vs. 29.1%, $p < 0.001$), no independent association for use of RAAS with mortality was found after adjusting for hypertension and other risk factors.

Discussion

According to available research, this is the largest cohort of hospitalized patients with COVID-19 outside the Hubei province that proves the incremental value of myocardial injury on admission for predicting all-cause 30 day mortality. This has been proved by a model which includes classical predictors, a second model including an index accounting for comorbidities, age and a propensity score analysis. According to the present data, combining the CCI (which is readily available for clinicians) with the presence of myocardial injury can classify patients into three risk groups (high, intermediate and low) with clearly distinct 30-day mortality (Fig. 2B).

In contrast to previous studies, time-dependent ROC curves were estimated to evaluate if the determination of cTnI provides additional information over other accessible clinical information. Proving this incremental value is crucial if a systematic determination of cTnI is being considered.

In the current study up to 1 in every 5 COVID-19 patients presented with myocardial injury. This finding is consistent with previous observations [2, 8–10]. The mechanism of troponin elevation is not yet clearly understood and evidence in this matter has yet to emerge. Whether it is a systemic consequence of a patient's hemodynamic status and hypoxia or direct myocardial damage is subject to debate. Inflammatory infiltration of the myocardial tissue by the virus has been proposed by some investigators [20, 21]. Another hypothesis is that the cytokine storm syndrome may provoke subclinical diastolic left ventricular impairment by itself [22].

Comorbidities are prevalent in patients hospitalized because of COVID-19, establishing a possible confounding factor with regards to cTnI elevation [2, 23]. However, the present results prove otherwise. The CCI is a validated clinical score that has demonstrated its usefulness both in a chronic and acute setting. It is related to the mortality of sepsis, pneumonia and seasonal influenza [13, 24–27]. In the cardiovascular acute setting, it has also been used as a reliable prognostic tool in situations such as acute myocardial infarction [28].

In the present cohort the presence of myocardial injury was significantly associated with an increased mortality risk, an observation that was consistent among all patient subgroups. Even in patients with low prevalence of comorbidities, such as patients with a CCI below 4, cTnI maintained its prognostic value. Use of cTnI among low-risk individuals reclassified 6.5% of patients, assimilating their predicted 30-day mortality risk to that of higher-risk individuals (from 10.1% to

Table 4. Evaluation of the incremental value of myocardial injury to the multivariate model.

	Estimate (95% CI)	P
C-statistic multivariate Cox model with myocardial injury and CCI	0.775 (0.739–0.811)	–
C-statistic multivariate Cox model without myocardial injury	0.756 (0.720–0.792)	–
ΔC-statistic	0.019 (0.001–0.037)	0.025
Continuous net, %	35.2 (0.4–42.5)	0.047
Integrated discrimination improvement index	0.034 (0.009–0.073)	< 0.001

CCI — Charlson comorbidity index; CI — confidence interval

28.3%). Similarly, the use of cTnI among patients with a CCI ≥ 4 reclassified 40.1% of them as very high risk (with a predicted mortality that shifted from 36.1% to 47.0%). Among those patients who died, 48.6% had presented with myocardial injury. Therefore, troponin elevation may be interpreted as an early warning sign with impending clinical implications, identifying those patients who might require careful patient monitoring.

Area under the ROC curve (AUC) is a popular measure of the incremental discrimination provided by a risk factor in a prediction model. However, the change in the area under the curve (ΔAUC) strongly depends on the baseline model. As demonstrated by Pencina et al. [29], a new predictor with a strong effect added to a good baseline model may result in a miniscule ΔAUC. Two other indexes have been proposed to measure the improvement in discrimination: the IDI and the cNRI, which are less dependent on the strength of the baseline model. Including cTnI in the model raised the AUC by 0.02 and the cNRI was 35.2%.

Given this incremental value, cost considerations should be studied before systematically recommending the determination of cTnI in patients with suspected COVID-19. Until then and according to the present data, cTnI could be used to aid physicians in classifying patients in the emergency department, especially those who are severely ill and might require closer vigilance and more intensive therapies.

The present study was executed on earlier phases of the pandemic, and most patients were treated with hydroxychloroquine. This agent has been recently been identified as being ineffective and even potentially harmful in COVID-19 patients [30]. Notwithstanding it was not thought to have any plausible interactions on the results of the current investigation.

Recently, it has been criticized that prediction models published during the current COVID-19 outbreak are poorly reported and sometimes lack statistical rigor [3]. Herein, an effort was made to adhere to the TRIPOD (transparent reporting of a multivariable prediction model for individual prognosis or diagnosis) reporting guidelines in order to minimize the risk of bias.

Limitations of the study

First, this is an observational single-center study and interventions were indicated by the treating physicians; however, adherence to the local consensus protocol resulted in uniform treatment choices and has made cTnI values available in the quasi-totality of patients. Secondly, the effect on downstream testing has not been evaluated, which may limit the universalization of the findings. Also, restrictions inherent to the emergence of an infectious outbreak limit the availability of some data. Last, because of the necessity of prompt and robust scientific data during the current outbreak, some observations were censored at the end of the observational period; given that less than 10% of patients remained hospitalized at the end of follow-up, no relevant variations of the outcome analysis might be expected.

Conclusions

Myocardial injury is strongly associated with all-cause mortality within 30 days in hospitalized patients with confirmed COVID-19, even after adjusting for comorbidities and other possible cofounders. Its inclusion in multivariate prediction models significantly enhanced their performance. Determination of cardiac troponin I on admission improves risk-stratification and its elevation is a caveat that should raise awareness of the possibility of adverse outcomes.

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Conflict of interest: None declared

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VIA MEDICA

ORIGINAL ARTICLE

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Resuscitation of the patient with suspected/ /confirmed COVID-19 when wearing personal protective equipment: A randomized multicenter crossover simulation trial

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Abstract

Background: *The aim of the study was to evaluate various methods of chest compressions in patients with suspected/confirmed SARS-CoV-2 infection conducted by medical students wearing full personal protective equipment (PPE) for aerosol generating procedures (AGP).*

Methods: *This was prospective, randomized, multicenter, single-blinded, crossover simulation trial. Thirty-five medical students after an advanced cardiovascular life support course, which included performing 2-min continuous chest compression scenarios using three methods: (A) manual chest compression (CC), (B) compression with CPRMeter, (C) compression with LifeLine ARM device. During resuscitation they are wearing full personal protective equipment for aerosol generating procedures.*

Results: *The median chest compression depth using manual CC, CPRMeter and LifeLine ARM varied and amounted to 40 (38–45) vs. 45 (40–50) vs. 51 (50–52) mm, respectively ($p = 0.002$). The median chest compression rate was 109 (IQR; 102–131) compressions per minute (CPM) for manual CC, 107 (105–127) CPM for CPRMeter, and 102 (101–102) CPM for LifeLine ARM ($p = 0.027$). The percentage of correct chest recoil was the highest for LifeLine ARM — 100% (95–100), 80% (60–90) in CPRMeter group, and the lowest for manual CC — 29% (26–48).*

Conclusions: *According to the results of this simulation trial, automated chest compression devices (ACCD) should be used for chest compression of patients with suspected/confirmed COVID-19. In the absence of ACCD, it seems reasonable to change the cardiopulmonary resuscitation algorithm (in the context of patients with suspected/confirmed COVID-19) by reducing the duration of the cardiopulmonary resuscitation cycle from the current 2-min to 1-min cycles due to a statistically significant reduction in the quality of chest compressions among rescuers wearing PPE AGP.* (Cardiol J 2020; 27, 5: 497–506)

Key words: chest compression, cardiopulmonary resuscitation, quality, COVID-19, SARS-CoV-2, medical simulation

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Introduction

The current coronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic which causes the disease as defined by the World Health Organization (WHO): COVID-19 represents a challenge for medical personnel, specifically including those who are particularly exposed to this type of patient [1]. Since the appearance of the first cases in China in December 2019, the virus has spread around the world. As of 1 May 2020, the number of confirmed infections worldwide has reached 3,260,373, including 233,996 deaths from the virus. The virus is transmitted from human to human by droplets [2, 3]. Therefore, medical personnel for patients with suspected/confirmed COVID-19 should use full personal protective equipment (PPE) for aerosol generating procedures (AGP) to reduce the risk of infection [4–6]. Yang et al. [7] indicated that in COVID-19-infected patients, comorbidities and the diagnosed underlying diseases include: hypertension, respiratory system and cardiovascular diseases may be a risk factors for severe compared with a non-severe course of the disease. Considering the above, as well as a mortality rate of nearly 5.4%, medical personnel may have to undertake resuscitation procedures on such a person.

Resuscitation guidelines are published by, among others, the European Resuscitation Council (ERC) [8, 9] or the American Heart Association (AHA) [10, 11]. On 24 April 2020 ERC published guidelines for conduct in COVID-19, which indicates the need to use personal protective equipment during resuscitation [12], but reference was not made to the impact of PPE AGE on the quality of resuscitation and thus the possibility of changing the resuscitation algorithm. However, as studies indicate, PPE may hinder medical procedures [13–15]. Chest compression systems including automatic chest compression devices (ACCD) or cardiopulmonary resuscitation (CPR) feedback devices which may be helpful in this regard. In the case of ACCD, CPR guidelines do not recommend their routine use. Resistance from the main medical community are based on the belief that ACCD causes more chest damage than manual chest compression (CC). Studies by Koster et al. [16] LUCAS suggest that a chest compression device does not cause significantly more serious or life-threatening visceral damage than manual CC.

The aim of the study was to evaluate various methods of chest compressions in a patient with suspected/confirmed SARS-CoV-2 infection conducted by medical students wearing full PPE for AGP. The hypothesis herein, is that the chest compression with LifeLine ARM was superior to CPRMeter as well as manual chest compression.

Methods

Study design

A multicenter, randomized, singe-blinded, crossover simulation study was conducted to evaluate chest compression quality of patients with suspected/confirmed COVID-19 by medical students wearing PPE for AGP. Study protocol was approved by Institutional Review Board of Polish Society of Disaster Medicine (Approval no. 09.01.2020.IRB). The study was conducted in medical simulation centers at Lazarski University (Warsaw, Poland) and Poznan University of Medical Science (Poznan, Poland) in February 2020.

Participants

The sample size was based on expected differences in time to intubation and calculated with G × Power 3.1 using the two-tailed t-test (Cohen's d = 0.8, alpha error = 0.05, power = 0.95). It was determined that a minimum of 32 participants were required for a pair-wise comparison of the samples. 35 medical students were recruited who had successfully completed an advanced cardiovascular life support (ACLS) course. Written voluntary informed consent was obtained from each participant prior to the study.

Equipment and materials

Two devices were used in the present study:

- CPRMeter feedback device (Laerdal, Stavanger, Norway), which is an accelerometer device. Placed in the middle of the chest and pressed by a rescuer, it shows the correctness of the rate of chest compressions, the depth of compressions as well as chest recoil [17, 18];
- LifeLine ARM automatic chest compression device (Defibtech, LLC, Guilford, CT, USA), which allows for automatic chest compression in two modes: 30:2 and in an asynchronous mode [19].

The reference method was manual chest compression.

To simulate a patient with suspected/confirmed COVID-19 requiring CPR, Resusci Anne Advanced SkillTrainer manikin (Laerdal, Stavanger, Norway) was used, which was placed on the floor in a brightly lit room.

Figure 1. Rescuer with personal protective equipment for aerosol generating procedures.

The participants were dressed in a ProChem I F suit providing protection against organic and inorganic chemicals in high concentrations and against particles less than 1 μm in diameter. This suit also protects against biological hazards and toxic agents and is often used during the current COVID-19 pandemic. To simulate real actions against a SARS-CoV-2 patient, the participants additionally wore a protective mask with FFP2 filter, protective goggles and a visor as well as double nitrile gloves (Fig. 1).

Interventions

All participants completed a brief questionnaire consisting of demographic information (age, sex). Before starting this trial, instructors gave medical students lectures for 30 min about the risks associated with SARS-CoV-2 coronavirus and how to perform CPR using the methods to be tested. The participants, wearing PPE AGP, had to conduct a 2-min cycle of continuous chest compressions in adults. In order to achieve the desired effect and focus only on parameters related to chest compressions, the scenario where the patient was intubated was foreseen, which made it possible to conduct continuous chest compressions. Chest compressions were performed using three methods: (A) Manual CC, (B) compression using the CPRMeter feedback device, (C) compression using the LifeLine ARM system.

Both the sequence of participants and chest compression methods were random. The ResearchRandomizer program was used for this purpose. Participants were divided into three groups. The first group started compressions using the manual method, the second using CPRMeter and the third using LifeLine ARM. After a 2-min CC cycle, the participants had a 2-h break and then performed chest compressions using another method. A detailed randomization procedure is shown in Figure 2.

Measurements

All parameters were recorded using SkillReporter software (Laerdal, Stavanger, Norway) attached to the simulator. Additionally, in order to analyze the parameters at intervals of 20 s, the parameters were recorded in real time using GoPro HERO 5 Black camera (GoPro, Inc., CA, USA). The parameters such as: depth of CCs, rate of CCs and degree of chest recoil were analyzed. The parameters as indicated by the ERC and AHA guidelines were employed, according to the depth of CCs of an adult should be in the range of 50–60 mm, a compression rate should be from 100 to 120 compressions per minute (CPM), was used as reference values [8, 10].

Following the completion of this scenario, the participants were asked to grade each chest compression method based on the fatigue according to visual-analogue scale (VAS) (1 = no fatigued, 100 = extremely fatigued) in the relevant scenario, but they discouraged from an overall ranking of the devices.

Statistical analysis

The data were compiled using a standard spreadsheet application (Excel, Microsoft, Redmond, WA, USA) and were analyzed using the Statistica version 13.3EN (Tibco Inc, Tulusa, OK, USA). Data were blinded from the team interpreting the results. All participant and chest compression parameter data were summarized descriptively. Categorical data are presented as raw numbers and as frequencies, and continuous and ordinal data are presented as the median and interquartile range (IQR). The Friedman test was used for intra-group analysis, and for a pairwise comparison, the Wilcoxon signed-rank test was used. In all analyses, a significance level $p < 0.05$ was used.

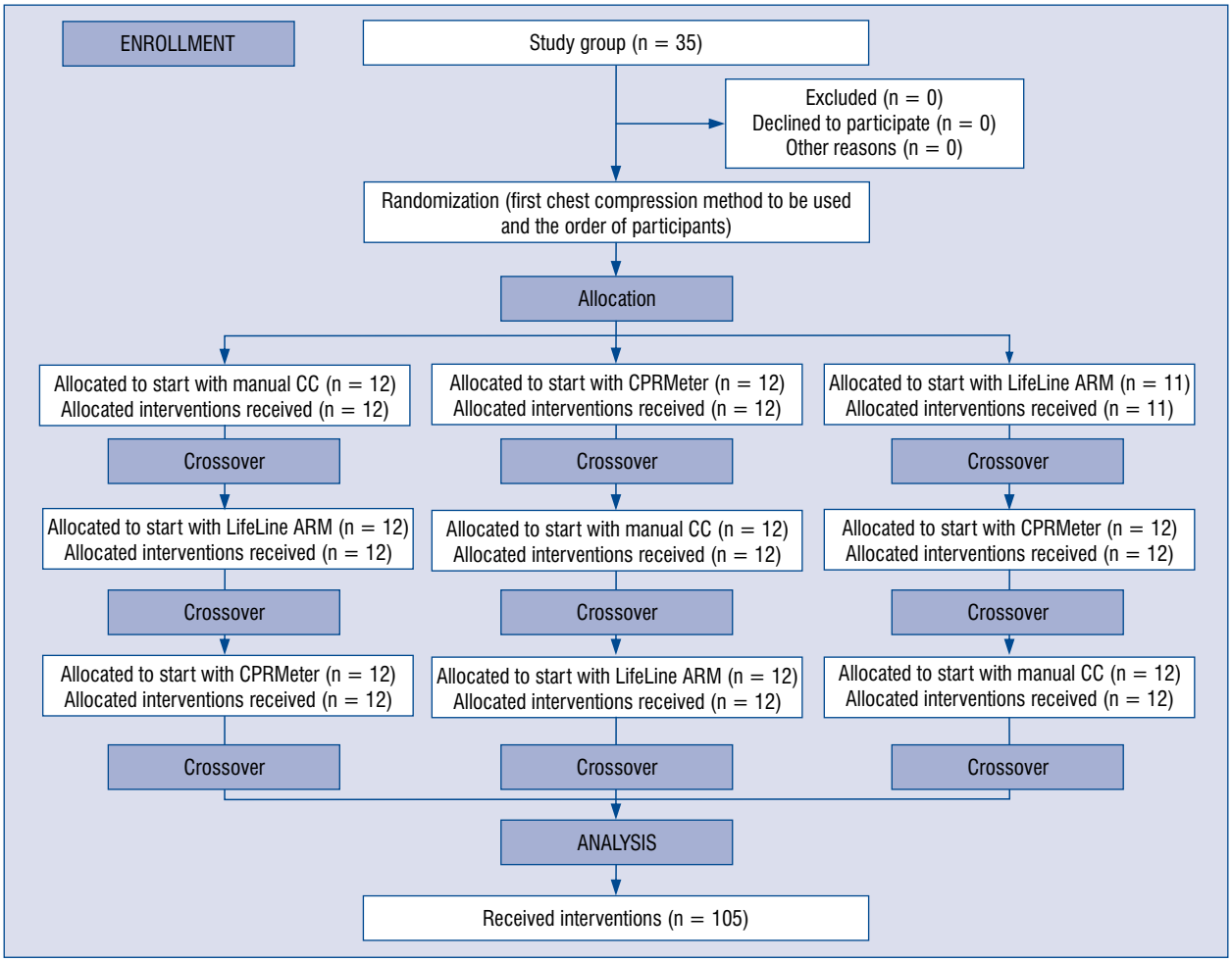

Figure 2. Randomization flow chart; CC — chest compression.

Table 1. Comparison of chest compression (CC) quality parameters.

Parameter	Chest compression technique			P
	Manual CC	CPRMeter	LifeLine ARM	
Chest compression depth	40 (38–45)	45 (40–50)	51 (50–52)	**0.002**
Chest compression rate	109 (102–131)	107 (105–127)	102 (101–102)	**0.027**
Correct chest recoil	29 (26–48)	80 (60–90)	100 (95–100)	**< 0.001**

Results

Thirty-five medical students after an ACLS course were enrolled. There were no exclusions in the present study.

Chest compression parameters

Data on the quality of 2-min CCs are presented in Table 1. Analysis of the quality of 2-min CCs showed statistically significant differences in the depth of CCs performed manually, using CPRMeter and LifeLine ARM (40 mm [38–45] vs. 45 mm [40–50] vs. 51 mm (50–52), respectively; p = = 0.002). Statistically significant differences in chest compression depth between manual chest compressions and CPRMeter (p = 0.031) and LifeLine ARM (p < 0.001) were shown. The difference was also observed between CPRMeter and LifeLine ARM (p = 0.002; **Suppl. Table 1**).

Compression rates for manual CC was 109 (IQR 102–131) CPM, 107 (IQR 105–127) CPM for CPRMeter feedback device, and 102 (IQR 101–102)

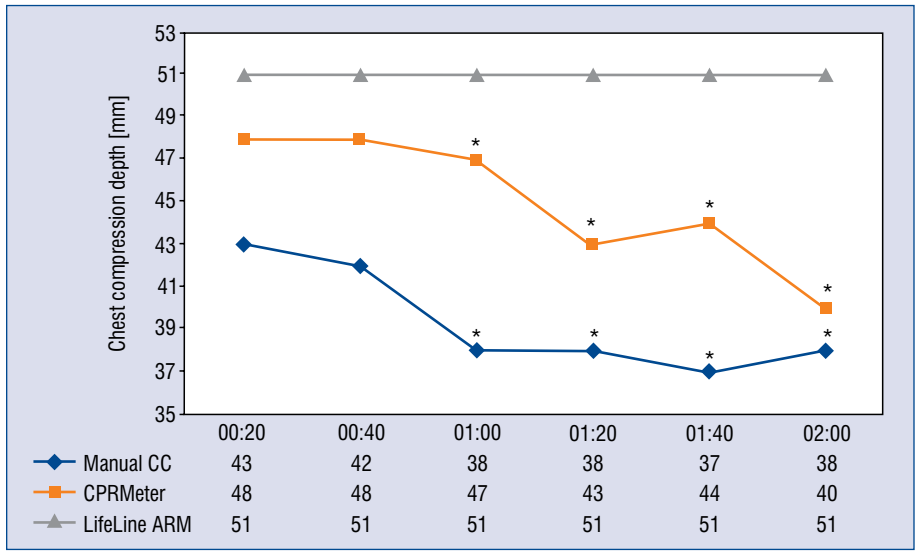

Figure 3. Chest compression (CC) depth parameters relative to time intervals; *Significant difference ($p < 0.05$) compared to the time of 20 s of an appropriate CC technique.

CPM for LifeLine ARM ($p = 0.027$). As in the previous parameter, statistically significant differences were observed between manual compression and CPRMeter ($p = 0.047$), manual compression and LifeLine ARM ($p = 0.001$), and between CPRMeter and LifeLine ARM ($p = 0.006$).

The best chest recoil was observed with LifeLine ARM systems — 100% (IQR 95–100), followed by CPRMeter — 80% (IQR 60–90), and the lowest for manual CC — 29% (IQR 26–48). These differences were statistically significant ($p < 0.001$). Two-sided analysis showed statistically significant differences in the percentage of correct chest recoils between manual CC and CPRMeter ($p < 0.001$), manual CC vs. LifeLine ARM ($p < 0.001$) as well as between CPRMeter and LifeLine ARM ($p < 0.001$).

Chest compression quality in 20-s periods

An analysis of the depth of chest compressions carried out in 20-s intervals is shown in Figure 3. Statistical analysis showed a significant reduction in the depth of CCs above 60 s for both manual CC and CPRMeter.

The chest compression rate showed statistically significant differences for manual CC and CPRMeter groups (Fig. 4).

The percentage of correct chest recoils for manual CC was significantly reduced after only 60 s of CPRMeter (Fig. 5). Percentage of correct chest recoils in LifeLine ARM remained the same throughout the entire chest compression period.

Fatigue VAS score

The degree of fatigue of study participants performing CCs based on VAS score when using manual CC, CPRMeter and LifeLine ARM groups was varied and were observed accordingly 75 (IQR 45–90) vs. 80 (IQR 50–90) vs. 20 (IQR 20–30) points ($p = 0.002$). There was statistically significant differences in degree of fatigue between manual chest compression and LifeLine ARM ($p < 0.001$), and between CPRMeter and LifeLine ARM ($p < 0.001$).

Discussion

Recent guidelines of the ERC as well as the AHA indicate a direct impact of high-quality CC on the effectiveness of resuscitation [8, 10] and thus, the return of spontaneous circulation and reduction of neurological deficits caused by hypoxemia.

During CPR, the need to interrupt CCs to provide synchronous ventilation prevents blood flow continuity, reducing the possibility to ensure high-quality CPR and have a negative impact on perfusion and patient outcome [20, 21]. In this study, continuous CCs were performed because, as indicated by ERC and AHA guidelines, the key role during CPR is to minimize pauses in CCs [8, 10]. In the case of patient intubation, continuous (asynchronous to emergency ventilation) CCs are possible [22]. As numerous studies indicate, it is the most effective method, because by eliminating long pauses accompanying rescue breathing improves

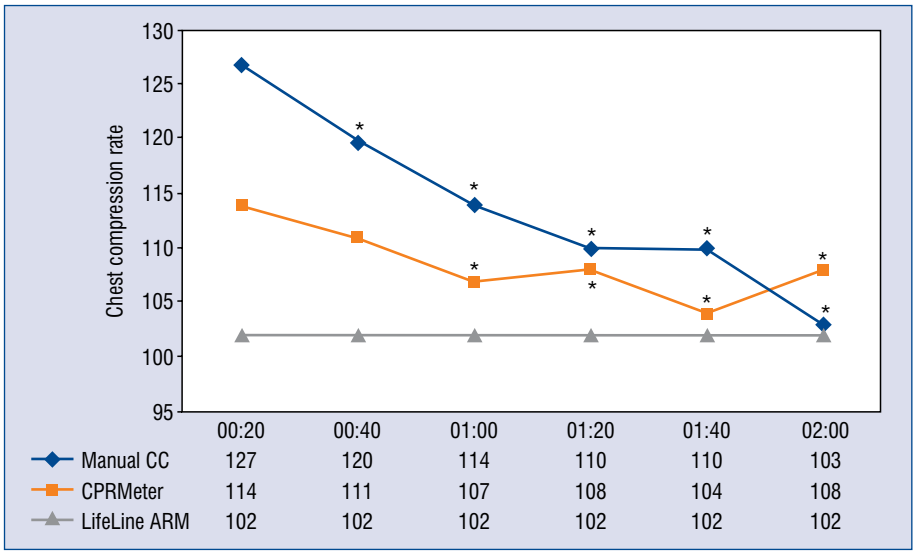

Figure 4. Chest compression (CC) rate parameters relative to time intervals; *Significant difference ($p < 0.05$) compared to the time of 20 s of an appropriate CC technique.

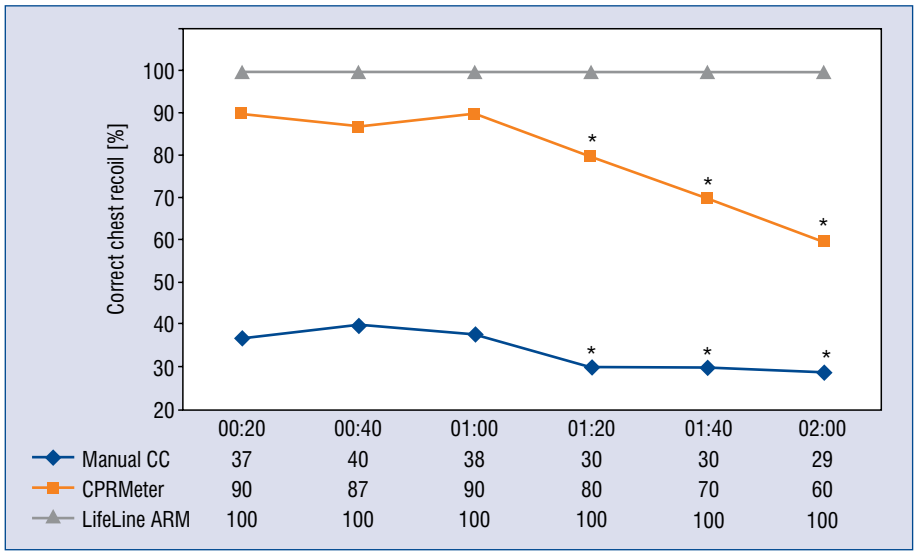

Figure 5. Percentage of correct chest recoil parameters relative to time intervals; *Significant difference ($p < 0.05$) compared to the time of 20 s of an appropriate chest compression (CC) technique.

perfusion pressure [22–24]. Continuous chest compression, as indicated by Heidenreich et al. [23] resulted in more adequate compressions per minute than standard CPR for the first 2 min of CPR. However, as the duration of the resuscitation increases, continuous chest compression technique leads to more fatigue for the rescuer. The reduction of fatigue may be influenced by the physical condition of the rescuer [25]. However, the application of PPE, as shown by numerous studies, may reduce the efficiency of medical procedures [26], starting with CCs [27], by obtaining vascular access [28, 29], ending with airway management [30, 31].

A factor influencing the quality of CPR is the depth of CCs [32]. For CPR without PPE AGP, the depth of CCs decreases after about 2 min of compressions [33].

In the current study there were statistically significant differences in the depth of CCs between the different methods of CCs. In the case of manual

CC and CPRMeter groups, a statistically significant decrease in the depth of CCs was observed after 1 min of resuscitation, which may have been caused by excessive fatigue of participants performing CCs as a result of using PPE AGP [13]. Other authors also point to the problem of reduced quality of CCs when using PPE [13, 27, 34]. In the present study, the CC depth during the use of ACCD was equal throughout the whole resuscitation process and was consistent with current CPR guidelines, due to the fact that the chest CC depth was performed automatically. This method of compression also allows CPR to be performed during patient transport to the hospital as well as during prolonged resuscitation [35, 36].

During CPR full chest recoil after each compression is independently associated with improved survival and is independently associated with improved survival and favorable neurologic outcome at hospital discharge after adult out-of--hospital cardiac arrest [37, 38]. Analysis of the obtained results showed that medical students dressed in PPE AGP perform manual CCs in an insufficient manner. The problem of incomplete chest relaxation is reduced when using CPRMeter. The results obtained are confirmed by other studies [39, 40]. Similar to the depth of compressions, chest recoil is significantly reduced after 1 min of continuous CC (in manual CC and CPRMeter groups). This may be due to fatigue of the rescuer and subsequent CC after each compression. CCs to the appropriate depth and then performing full chest recoil is a prerequisite for optimal perfusion pressure [24, 41].

The rate of CC is also an important element of high-quality CC. CPR guidelines recommend that CC should be performed at a rate of 100–120 CPM. Idris et al. [42] confirms that compression rates between 100 and 120 per minute were associated with the greatest survival to hospital discharge. A higher compression rate than 120 CPM may improve organ perfusion but does not increase survival. However, it may lead to faster fatigue of the rescuer, which consequently results in lower quality of CCs [43, 44]. Chen at al. [34] suggested that the use of PPE may reduce the rate of chest compression.

Cardiopulmonary resuscitation feedback devices facilitate CCs by showing real-time compression parameters [45, 46]. Iskrzycki et al. [47] in his study showed that visual real-time feedback device significantly improved quality of CPR performer by lifeguards. In contrast Wattenbarger et al. [48] stated that a targeted training intervention combined with real-time CPR feedback improved CC performance among health care providers. However, the use of such a device still requires force from the rescuer and also leads to fatigue. In the study, after 1 min of continuous CCs, rescuers dressed in PPE AGP were both statistically significant in reducing the depth of CCs and in reducing chest recoil. This may result in reduced effectiveness of the whole resuscitation process. Another solution aimed at improving the quality of CC is the automatic CC system. Taking into account the fact that the quality of CCs performed by medical personnel is in many cases insufficient [49], there can be a remedy for this problem. Analysis of the data obtained in this study showed that LifeLine ARM, an example of ACCD, performed CCs at the appropriate depth and at the programmed compression rate. As indicated by the studies Szarpak et al. [50], and Truszewski et al. [51] LifeLine ARM resuscitation using LifeLine ARM had significantly better quality compared to manual chest compressions.

The use of such systems is particularly important when paramedics are unable to perform high quality CPR — and this is the case for patients with suspected/confirmed COVID-19 when, due to the coronavirus, personnel must be equipped with PPE AGP.

Limitations of the study

There were several limitations in the present study. First, an adult manikin was used to simulate patients requiring CPR. Therefore, the quality of chest compressions may differ from that of CPR under real CPR. However, the choice of medical simulation as a research method was deliberate and was dictated by the fact that it is medical simulation that allows for full standardization of performed procedures without the risk of complications for a potential patient [24, 52, 53], moreover, in the current pandemic, conducting research — in particular randomized cross-over study under emergency conditions could endanger both the patient and the rescuer. The second limitation was to include only medical students in the study, however, this group may be involved in providing medical assistance in a disaster or emergency situation, hence an assessment of the possibility of CPR in PPE AGP is one of the key actions to determine an optimal method of CPR.

The study also has its strengths. Among them, was the randomized cross-over study design, as well as the fact that it was a multi-center study. Additionally, a single-blinded study was utilized, increasing its value. Another aspect supporting

this study is the fact that, according to available research, this is the first study comparing different methods of CC of patients with suspected/confirmed COVID-19 by rescuers wearing personal protective equipment for aerosol generating procedures.

Conclusions

In conclusion, according to the results of this simulation trial, ACCD should be used for CC of patients with suspected/confirmed COVID-19. In the absence of ACCD, it seems reasonable to change the CPR algorithm (in the context of patients with suspected/confirmed COVID-19) by reducing the duration of the CPR cycle for one rescuer from the current 2-min to 1-min cycles due to a statistically significant reduction in the quality of CCs among rescuers wearing PPE AGP. More studies on chest compression quality with PPE AGP should be conducted to confirm those data.

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Conflict of interest: Bernd W. Böttiger is European Resuscitation Council (ERC) Board Director Science and Research; Chairman of the German Resuscitation Council (GRC); Member of the, Advanced Life Support (ALS) Task Force of the International Liaison Committee on Resuscitation, Member of the executive committee of the German Interdisciplinary Association for Intensive and Emergency Medicine (DIVI); Associated Editor of the European Journal of Anaesthesiology (EJA), Co-Editor of "Resuscitation"; Editor of the Journal "Notfall + Rettungsmedizin". He received professional fees for lectures from the following companies: Medupdate GmbH, "Forum für medizinische Fortbildung (FomF)", Baxalta Deutschland GmbH, Bayer Vital GmbH, ZOLL Medical Deutschland GmbH, C.R. Bard GmbH, GS Elektromedizinische Geräte G. Stemple GmbH. Others authors have no potential conflict of interest relevant to this article.

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Elliptical stretch as a cause of side branch ostial compromise after main vessel stenting in coronary bifurcations: New insights from numerical analysis

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Abstract

Background: *The side branch (SB) compromise after main vessel (MV) stenting remains a significant problem in coronary bifurcation treatment. Currently the two major hypotheses for the mechanism of SB compromise are carina shift from MV into the SB and plaque shift into the ostium of side vessel. It is proposed herein, SB ostial deformation leading to reshaping of the ostium from circle to ellipse is a third possible mechanism. In the current study, the theoretical effects and correlation of ostial deformation with fractional flow reserve (FFR) is explored.*

Methods: *Based on angiographic measurements and theoretical analysis formulas, three different SB ostial areas using circular ostial shape assumption and elliptical ostial shape assumption were calculated. Three different types of ostial areas with FFR values after MV stenting in 49 patients from the FIESTA registry were compared and analyzed.*

Results: *It was found that there is significant overestimation of stenosis severity when estimated by the circle formula, than with the ellipse formula — ASc vs. ASds with 25% ± 13%, $p < 0.001$, ASc vs. ASmld with 9% ± 10%, $p < 0.001$. The elliptical shape assumptions provide more accurate ostial area stenosis, which correlates better with FFR. This finding is more significant in less severe stenosis (< 70% area stenosis) than in a more severe one.*

Conclusions: *A third possible mechanism of SB compromise after MV stenting of coronary bifurcation stenosis is elliptical ostial deformation at the ostium of SBs. The ostial area, calculated based on elliptical assumption correlates better with FFR, than area stenosis calculated with the traditional circular formula.* (Cardiol J 2020; 27, 5: 507–517)

Key words: coronary bifurcation, side branch ostium compromise, elliptical ostial stretching

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Introduction

There have been major improvements in treatment of coronary bifurcations in recent years [1]. Nowadays, there is much more known about stent characteristics which are important in achieving good procedural results. With the advent of drug-eluting stents (DES) the problem of restenosis was largely reduced. However, the main reason which makes coronary bifurcation so difficult to treat still persists — namely, side branch compromise which is the appearance of high grade ostial stenosis at the ostium of the side branch (SB), limiting vessel inflow after implantation of a stent in the main vessel (MV). In the most severe form of SB compromise, the vessel can occlude leading to a different size periprocedural myocardial infarction with different prognostic implications, depending on amount of subtended myocardium by the SB. There is still uncertainty about the mechanisms of SB compromise after MV stenting in coronary bifurcation lesions. There are currently two major hypotheses: 1) Plaque shift from MV into the SB and 2) Carina shift due to pushing of carina tip into the ostium of side vessel [1]. Based on theory, phantom elastic models and then on angiographic analysis from the patient cohort, demonstrated herein, that carina displacement is probably the most important mechanism for SB stenosis [2–4]. Besides possible plaque shift (from proximal MV to SB ostium and plaque redistribution of SB plaque in a circumferential direction), there is however, another potential mechanism; i.e., ostial deformation resulting in reshaping of side vessel ostium from ostial circle initially to ostial ellipse after stenting [3]. These potential changes were recently reported in human coronary bifurcation after stenting of MV [5, 6]. Thus, the present study proposed this as a third possible mechanism for SB compromise, which can operate in conjunction with carina displacement and plaque shifting. Here, the theoretical effects are explored and a correlation of these possible deformational effects with fractional flow reserve (FFR), serve as a current standard for assessment of stenosis severity [7].

Methods

A theoretical analysis was performed on the potential changes at the SB ostium after MV stenting. Formulas were derived for minimal lumen diameter at SB opening after stenting based on an assumed elliptical stretch, with constant vessel circumference irrespective of vessel deformations. An angiographic analysis was performed to measure minimal lumen diameter and reference diameters of the bifurcation region from a patient cohort, with FFR during coronary bifurcation intervention being simultaneously measured.

Based on angiographic measurements and using formulas from theoretical analysis, three different SB ostial areas were calculated which were then compared with FFR values after MV stenting. First, a circular ostial shape at SB ostium was assumed after stenting using the formula: $\mathbf{A_c = \pi.ds^2/4}$, where ds is reference side branch vessel diameter as measured from quantitative coronary assessment (QCA). This is a standard calculation used in two-dimensional QCA software packages. Second, we assumed elliptical ostial shape of SB ostium after MV stenting. The calculation of the ostial area uses the ellipse area formula $A = \pi.a.b$, where a is the ostial minimal lumen diameter as a minor semi axis. This minor semi axis "a" equivalent of SB ostial minimal lumen diameter, as measured from standard QCA. The major semi axis (b) was calculated using formulas 3'-12' (see below), replacing k (stretching coefficient) with its equivalent (ds/2)/a (where ds is SB reference diameter and a is ostial elliptic minor axis after stent placement in the MV). The SB diameter, ds, was taken as a reference in those calculations. The respective area stenosis was calculated as ASds = (1-Ae1/Asb) × 100, where ASds is ostial elliptic area stenosis of the SB, Ae1 — SB calculated ostial area, Asb — reference SB vessel area (calculated based on vessel diameter 1 mm distal from the end of visually diseased end of plaque segment). For the third calculation of SB ostial area after stenting, the same assumptions and formulas were used as in the second, but as a reference diameter instead of SB reference diameter the SB ostial minimal lumen diameter before stenting was used (i.e. this is the minimal lumen diameter before stenting, as measured from QCA). The corresponding area stenosis was labeled ASmld = (1-Ae2/Asb) × 100, where ASmld is ostial area stenosis (in percentages), Ae2 — ostial SB area calculated according to the above assumptions, Asb — as above.

All three calculated areas were correlated with FFR measured in SB after stenting to determine functional significance of ostial stenosis. In theory, the flow through SB ostium should be proportional to its cross-sectional area and the subtended myocardium. Hence, a better estimate of real cross-sectional area of side vessel opening should correlate better with FFR.

Theoretical analysis

A model of bifurcation with normal opening of proximal MV was assumed, with a diameter dp at the point of distal MV and SB divergence. The SB has a circular opening in a plane perpendicular to the plane of bifurcation. The diameters of distal MV and SB are denoted as dm and ds, accordingly. At the point of connection of the three tubes there is a beveling region with a length equal to SB tube diameter. The vessels are assumed to be deformable straight tubes at the region of interest. No other assumptions were made regarding the model (Fig. 1A). After stent placement in MV across the SB, the stent stretches a bevel region of bifurcation causing "squeezing" SB ostium and ellipse formation at the opening [4]. Those changes were described in experimental elastic model by our group and currently reported to occur in human patients with optical coherence tomography observations [5, 6].

The SB minimal lumen diameter was calculated, SB ostial area and respective derived parameters. It was assumed that after stenting MV, the SB stretched to ellipse geometry at the ostium. The short axis of a newly formed ellipse was parallel with SB long axis and the short axiswas in a perpendicular direction (Fig. 2). This new elliptic short axis is a minimal lumen diameter for SB ostium and the area of ellipse relative area of reference cross-section of the SB is a lumen area stenosis of the ostium. If the vessel wall is inelastic and the vessel perimeter remains constant during simple deformations without circumferential stretching forces, the minimal (short) ellipse diameter, a, is determined from the extent of stretching (lateral increase) of SB vessel major axis b. The major axis can be expressed as a multiple of SB reference diameter: a' = k.ds/2, where ds is the SB diameter (measured from QCA side branch reference vessel diameter) and k is the stretch coefficient. The stretch coefficient can vary to two maxima — k1 = dm/ds or k2 = dp/ds (dm — MV distal diameter, dp — proximal MV diameter), depending on the choice of stent diameter. According to the above assumption of constant vessel perimeter and knowing the extent of ostial stretch (expressed as the value of k), the minimal diameter at the ostium was calculated. Using elementary integration methods, the perimeter S(a,b) of the ellipse defined by (x/a)+(y/b) = 1, is given by:

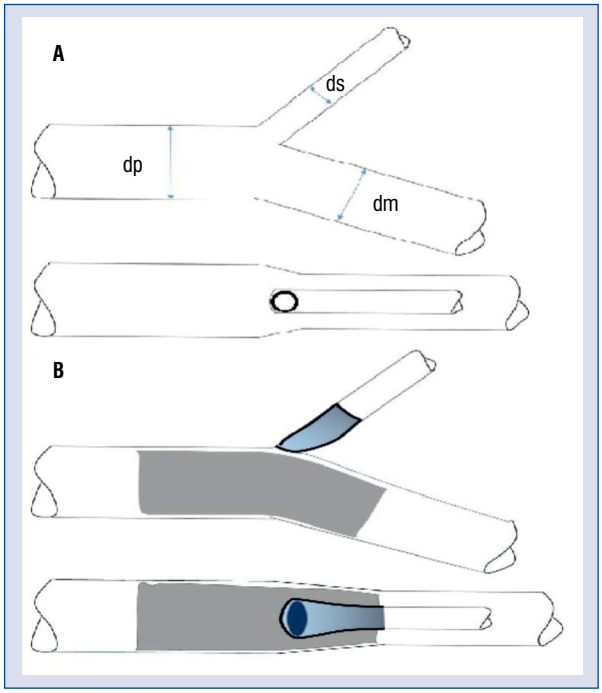

Figure 1. A. Model of bifurcation before stent placement; dp — proximal main vessel diameter; dm — distal main vessel diameter; ds — side branch vessel diameter; **B.** Lateral and axial views of bifurcation region after stent placement. The stent (gray rectangle) pushes the carina to the side branch ostium and causes widening and stretching of beveling region, which in fact stretches side branch ostium in a perpendicular direction of the main vessel axis. This leads to an elliptical shape of branch ostium.

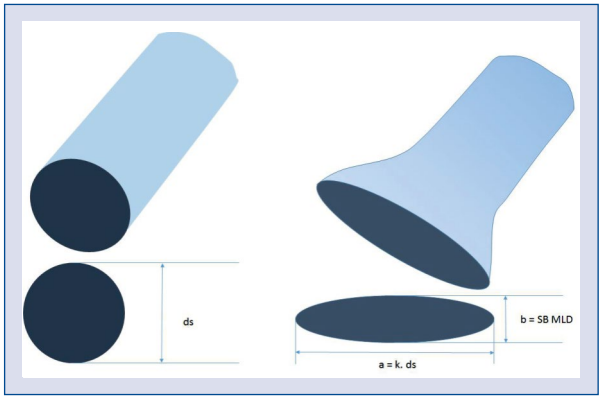

Figure 2. Idealized view of side branch (SB) ostium before and after stent placement; i.e., before and after stretching. a and b are major and minor axes of newly formed ellipse; ds — side branch reference diameter; k — stretching coefficient, being the diameter of ellipse after transformation from a circle; MLD — minimal lumen diameter.

$S(a, b) = 4aE(e^2)$, where $e = \sqrt{a^2 - b^2}/a$ (1)

where E, the ellipse eccentricity, is given by:

$$E(x) = \int_0^{\pi/2} 1 - x.\sin^2\theta)^{1/2}\, d\theta \quad (2)$$

E is an elliptic integral of the second kind, which can be computed with numeric integration or by approximations. The problem with equation (1) is that E(x) is a transcendental function and its evaluation through an infinite series or fractions is computationally inefficient. Therefore, it was decided that some approximation formulas would be used, giving in the ellipse perimeter computation less than 1% error in comparison with exact computation [8–15]. For each formula below (denoted by numerical equation), we give a derivative formula (denoted by prime) for short axis semi diameter, based on values of SB diameter and stretch coefficient as independent variables.

$P = 2\pi\{[p.(a+b)/2]+[(1-p).\sqrt{(a.b)}]\}$, with $p = 3/2$ Optimized Peano (3)

$b = ds/9.\{6-7k/2+(2.\sqrt{(3k-2k^2)}\}$ (3')

$P = 2\pi\{(a^{3/2}+b^{3/2})/2\}^{2/3}$ Muir (4)

$b = ds/2.\{2-k^{3/2}\}^{2/3}$ (4')

$P = \pi\{3.(a+b)-\sqrt{[(a+3b)(3a+b)]}\}$ Ramanujan (5)

$b = ds/6.\{3-2k+\sqrt{(3+6k-5k^2)}\}$ (5')

$P = 2.\sqrt{[\pi^2 a.b + 4.(a-b)^2]}$ Seki (6)

$b = ds/16.\{k.(8-\pi^2) + \pi\sqrt{[k^2(\pi^2-16) + 16]}$ (6')

$P = 4.(a^s+b^s)^{1/s}$, $s = \ln 2/\ln(\pi/2) = 1.53492853566$ Marthens (7)

$b = ds/2.[(\pi/2)^s - k^s]^{1/s}$ (7')

$P = 4a + \{2.(\pi-2).a.(b/a)^{1.456}\}$ Rivera (8)

$b = ds/2.k.\{[(\pi-2k)/(k.(\pi-2))]^{0.6868}\}$ (8')

$P = 4\{[\pi.a.b + (a-b)^2]/[a+b]\}$ Rivera-Sykora (9)

$b = ds/8\{\pi+4k-2\pi k + \sqrt{[(4k\,\pi.(k-1)(\pi-4)) + \pi^2]}\}$ (9')

$P = 2.\pi\sqrt{\{[w.(a^2+b^2)/2] + [(1-w)(ab)]\}}$ QO1 (10)

$b = ds/2\{[(w-1).k] + \sqrt{[k^2(1-2w) + 2w]}\}$ (10')

The parameter w can be optimized, giving the best result at w = 1.007.

$P = \pi\sqrt{\{[2(a^2+b^2)]-[(a-b)^2/D]\}}$ QO2 (11)

$b = ds/2\{[-k+2\sqrt{(D(k^2(1-D) + 2D-1))}]/(2D-1)$ (11')

The parameter D gives optimal results with values between 2 and 3 (D=2.5 for present analysis).

$P = \varpi.\{(a+b)/2 + \sqrt{[(a^2+b^2)/2]}\}$ QO3 (12)

$b = ds/2[-4+k+4\sqrt{(2-k)}]$ (12')

All the above formulas at k = 1 (circular shape) reduce to a simple formula for circle perimeter with a radius equal to ds/2. There are certain limits of k values — in most of the cases it cannot be > 1.6. Therefore, being tested were the results for k varying between 1.1 and 1.5. The ostial elliptic area, $A_x = \pi.ds.b$ and SB reference circular area ($A_c = \pi.ds^2/4$), were compared to determine possible ostial percent area stenosis, $AS = (1-A_x/A_c) \times 100$. The ostial percent diameter stenosis was calculated as $DS = (1-b/ds) \times 100$. The derived eccentricity of the ostium of SB was expressed as e = a/b, where a and b are major and minor semi axes, respectively.

For practical calculations (see Results section) formula 5 (Ramanujan) was used for calculation of the area stenosis. For calculation of area stenosis after stenting numerical values were used from QCA as follows: for ASds minimal lumen diameter after stenting divided to SB reference diameter to derive parameter k = SBMLD/SBRVD were used; then this value was used to calculate parameter b in formula 5, and then the ostial area was calculated as $Ads = \pi.SBMLD.b$ For calculation of ASmld (see Results section) for calculation of parameter k the SBMLD before stenting was used: $k = SBMLD_{afterstent}/SBMLD_{beforestent}$, then the parameter b was calculated as described and the ostial area was calculated in the same way: $Amld = \pi.SBMLD.b$ According area stenosis is derived by dividing ostial area by SB reference area $A_c = \pi.ds^2/4$.

Angiographic analysis

Quantitative angiographic analyses were performed using commercially available software (Medis QCA version 5.0, Leiden, the Netherlands; Dicom Works version 3.1.5b, Paris). Catheter calibration was used in all cases. Bifurcation lesions were classified according to the visual Medina classification using an index of 1 for stenoses greater than 50% and an index of 0 for no stenosis. The changes of SB percentage diameter stenosis (SB%DS) before procedure, after stenting and at the end of percutaneous coronary intervention (PCI) were assessed. SB reference diameter, as well as minimal lumen diameters were measured before and after stenting, after giving 100 μg nitroglycerin intracoronary.

Procedures

Patients from the FIESTA registry were analyzed, which was a continuation of the FIESTA

study (Ffr vs. IcEcgSTA) [15]. Briefly, patients with stable or unstable angina were included. The inclusion criterion were angiographic bifurcation lesions in a native coronary artery with a diameter ≥ 2.5 mm and ≤ 4.5 mm and SB diameter ≥ 2.0 mm. Patients with ST-segment elevation myocardial infarction and those with non-cardiac co-morbidity conditions with a life expectancy of less than one year were excluded. PCI was performed according to current guidelines. Provisional stenting was the default strategy in all patients. Two guidewires were inserted into both distal MB and SB. Initial FFR and post-stenting FFR was performed using PrimeWire or PrimeWire Prestige (Volcano Corp., USA). For all FFR measurements, intracoronary adenosine was given in increasing doses of 60 μg, 120 μg, and 240 μg. The minimum value of FFR measurements was taken for analysis. Pre-dilatation of MV was mandatory. The SB balloon predilatation was left to operator discretion, regardless of the initial FFR values. All patients received double antiplatelet therapy with ADP-antagonist and acetylsalicylic acid for at least 12 months.

Statistics

Continuous data are presented as mean ± standard deviation. Differences between groups were examined with paired or unpaired t-tests as appropriate, with normal distributions. If the distribution was not normal, the Wilcoxon sign-ranked test and Mann-Whitney U-tests was performed. Analysis of variance (ANOVA) was used for multiple comparisons of data, when parameters were distributed normally. Otherwise, the Kruskall-Wallis test was performed. Correlation analysis as well as univariate regression analysis were performed to identify associates of "significant" cut-off value of FFR. For purposes of current analysis, test 0.80 were made cut-off values for FFR [7]. All univariate predictors with $p < 0.1$ were included in a multivariate model. Chi-square tests were applied for qualitative data. For determining of cut-off values for continuous parameters a receiver-operation curve analysis was performed, determining sensitivity and specificity of a given value. A $p < 0.05$ was accepted as statistical significance.

Results

Theoretical analysis

For the theoretical analysis that diameters of main branch vessel varying between the 2.5–4.0 mm range were assumed and side branch diameter varied between 1.5–3.0 mm. Figures 3 and 4 present the calculated percentage diameter stenosis and area stenosis based on elliptical ostial shape assumption and circular ostial shape assumption.

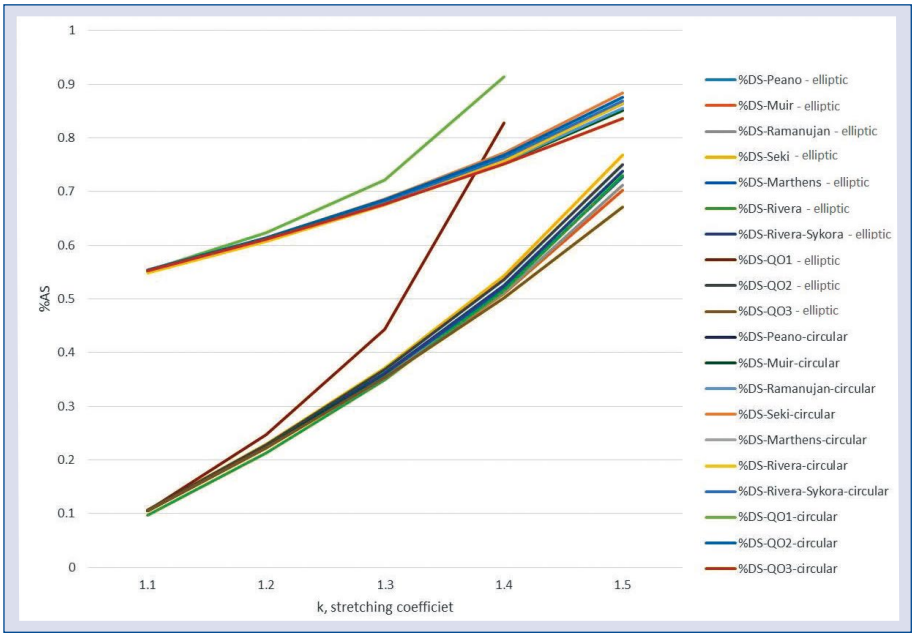

Figure 3. Percentage diameter stenosis change depending on coefficient of stretch. The upper curves represent %AS if ostial circular shape is assumed. There is considerable overestimation of stenosis severity with circular shape assumption.

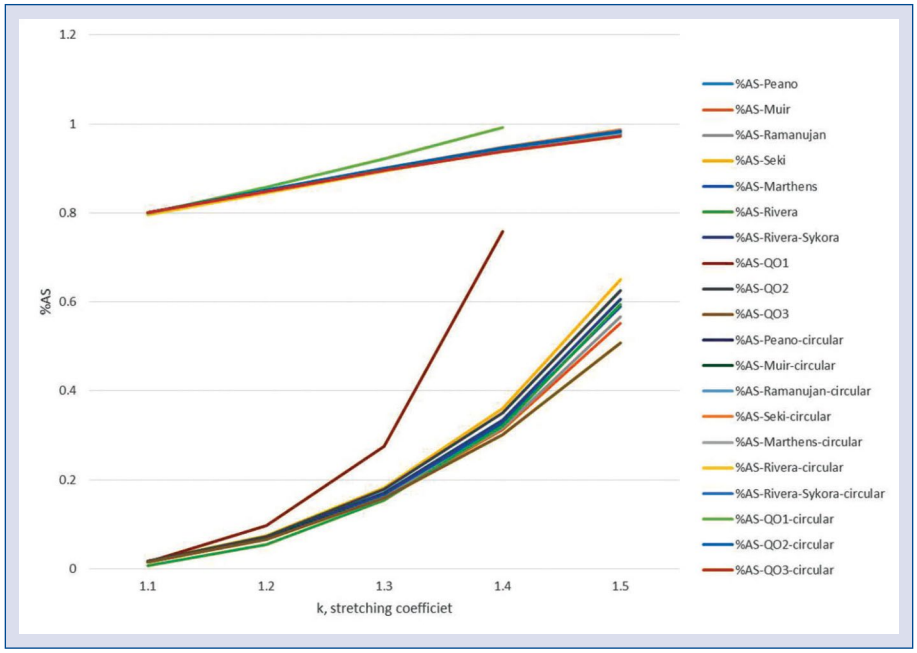

Figure 4. Percentage area stenosis change depending on coefficient of stretch. The upper curves represent %AS if an ostial circular shape is assumed.

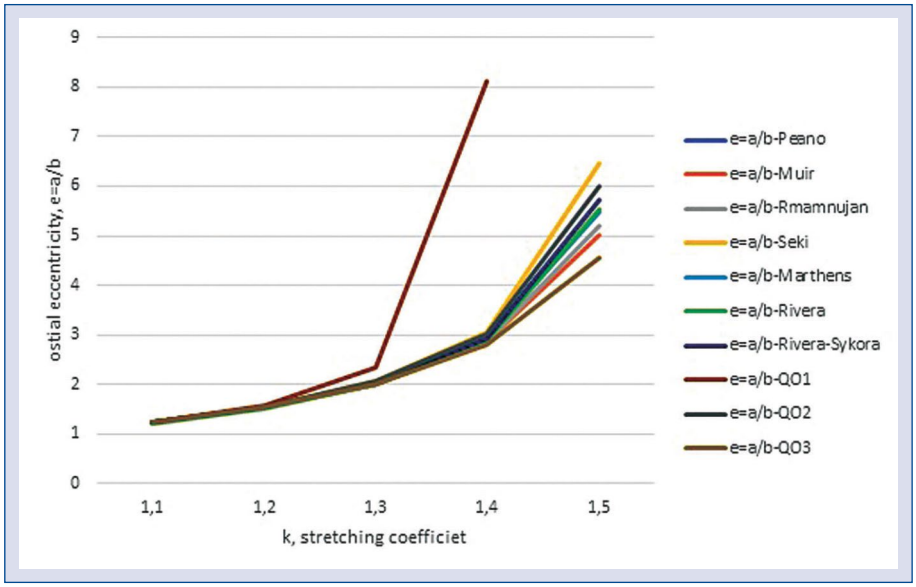

Figure 5. Ostium eccentricity. There is a striking increase when stretch is greater than 1.4.

With an increase in stretching coefficient, there is a reduction of overestimation (based on QCA data) of stenosis severity if circular shapes are assumed. The overestimation is larger for percentage diameter stenosis than for area stenosis (between 80% and 35% in absolute value), however, this means a significant difference in cross-sectional area of SB ostium. In high grade stenoses (> 90% diameter stenosis the differences between elliptical and circular calculated area stenoses were small. The quadratic optimization (Eqn. 1) gives larger deviations than the other formulas giving closer to circular approximation values for %DS and %AS at high stretch values. The eccentricity varies between 1.22 and 6, with a mean value of 2.64 ± 1.77 (Fig. 5).

Table 1. Clinical and demographic patient characteristics. Renal failure defined as calculated glomerular filtration rate according to the Cockcroft-Gault formula < 60 mL/min.

Patient characteristics	Entire group	No-SB predilatation (n = 31)	SB predilatation (n = 18)	P
Age [years]	66 ± 11	64 ± 12	65 ± 11	0.611
Sex — males	32 (66%)	21 (77%)	11 (61%)	0.232
Hypertension	49 (100%)	31 (100%)	18 (100%)	1
Hyperlipidemia	44 (90%)	28 (84%)	16 (89%)	0.637
Diabetes	23 (47%)	14 (45%)	9 (50%)	0.750
Renal failure	21 (43%)	13 (39%)	8 (44%)	0.562
Carotid artery disease	7 (14%)	4 (12%)	3 (17%)	0.336
Smoking	30 (61%)	19 (63%)	11 (61%)	0.891
Chronic lung disease	6 (12%)	2 (6%)	4 (22%)	0.109
Previous myocardial infarction	12 (24%)	7 (23%)	5 (28%)	0.749
Previous PCI	27 (55%)	16 (52%)	11 (61%)	0.529

PCI — percutaneous coronary intervention; SB — side branch

Since all formulas for calculated long axis ostial elliptical diameter give very close results (excluding QO2 formula), it was decided to use only the Ramanujan formula in the present calculations as it gives closest values to a mean value of all formulas for the derived parameters.

Clinical, angiographic and procedural characteristics

A total of 49 patients were included — all with stable angina or with recent onset of unstable angina, but with negative troponin. All patients had a significant (< 0.80) FFR in MV with or without significant FFR in side branches. The dominantly treated vessel was left anterior descending artery (n = 42, 86%) with diagonal branches, and the rest of the cases were circumflex artery with marginal branches (n = 5, 10%) and right posterior descending artery with its posterolateral branches. The SB was predilated in 37% of the cases, mainly because of angiographically appearing high-grade ostial stenosis. In all patients, the FFR in MV was ≤ 0.80, and the initial FFR value was ≤ 0.80 in 26 (53%) side branches. Eighteen side branches remained with FFR ≤ 0.80 after stenting, 8 of which were significantly obstructed (based on FFR) after stenting were not, 9 (18%) new branches became significantly stenosed and the rest, 14 (29%) remained insignificantly stenosed before and after stenting in MV. Only one patient had SB predilated despite non-significant FFR initial value. Interestingly, 10 (20%) patients, despite SB balloon dilatation, the stenosis remained significant after stenting (Table 1).

Relations with FFR measurements and ostial area stenosis: as mentioned in the Methods section, ostial area stenosis at SB ostium after stenting was calculated by using three groups.

- Group 1: Circular ostial shape at SB ostium after MV stenting was assumed. This is a standard estimation of SB ostial stenosis severity (circular area stenosis — ASc).
- Group 2: Elliptical ostial shape at SB ostium assumed after MV stenting — calculated with SB reference diameter, taken into account for long axis ellipse calculation according to formula 5 (Ramanujan) — ASds.
- Group 3: Elliptical ostial shape at SB ostium assumed after MV stenting, calculated with minimal lumen diameter at SB ostium before stenting, considered for long axis ellipse calculation (instead of ds, SBRVD, an ostial minimal lumen diameter at the ostium of SB is used) according to formula 5 (Ramanujan) – ASmld.

Each comparison was made for the entire group, and in groups with and without SB predilatation. In the group with SB predilatation, there were better correlations with FFR values with ASds (as the ostial area after balloon predilatation is assumed circular and closer to the reference vessel diameter and consequent transition circular-to-elliptic will operate according to a circular shape of the reference vessel). In group without SB predilataion, FFR will be better correlated with ASmld. In the last group, it was assumed that the circular ostial shape of initial SB minimal ostial diameter, which deforms to ellipse after stenting. In general, there was a significant change in

Table 2. Angiographic and procedural characteristics of patients.

	Entire group	No-SB predilatation	SB predilatation	P
MV RVD [mm]	3.36 ± 0.29	3.38 ± 0.27	3.28 ± 0.26	0.189
MV %DS [%]	51 ± 22	60 ± 21	58 ± 20	0.766
MV %DS [%], final	3 ± 9	2 ± 5	3 ± 9	0.614
MB RVD [mm]	2.97 ± 0.21	2.99 ± 0.25	2.96 ± 0.18	0.585
MB %DS [%]	61 ± 18	67 ± 13	71 ± 11	0.220
MB %DS [%], final	6 ± 16	2 ± 6	3 ± 1	0.308
SB RVD [mm]	2.51 ± 0.27	2.45 ± 0.29	2.53 ± 0.26	0.330
SB %DS [%]	52 ± 24	46 ± 24	71 ± 14	0.001
SB %DS [%], post stenting	67 ± 27	65 ± 27	82 ± 15	0.008
SB %DS [%], final	39 ± 33	42 ± 33	31 ± 36	0.299
SYNTAX score	12 ± 4	12 ± 4	14 ± 4	0.231
Multi-vessel disease	21 (43%)	14 (45%)	7 (39%)	0.677
Stent diameter [mm]	2.97 ± 0.36	2.97 ± 0.35	2.96 ± 0.38	0.930
Total stent length [mm]	46 ± 22	45 ± 24	48 ± 17	0.629
Stent implantation pressure [atm]	13 ± 1	13 ± 2	13 ± 3	0.318
FFR-MB, before stenting	76 ± 9	70 ± 10	71 ± 6	0.733
FFR-SB, before stenting	82 ± 9	81 ± 9	76 ± 11	0.100
FFR-SB, after stenting	78 ± 13	81 ± 13	72 ± 13	0.024
FFR-MB, final	88 ± 5	90 ± 4	90 ± 4	0.895
FFR-SB, final	90 ± 4	89 ± 5	87 ± 6	0.313

MB — main branch; MV — main vessel; SB — side branch; RVD — reference vessel diameter; mm — proximal MV reference vessel diameter in mm; MV %DS [%] — proximal MV percentage diameter stenosis; RVD [mm] — distal main branch reference vessel diameter in mm; MB %DS [%] — distal main branch percentage diameter stenosis; SB RVD [mm] — SB reference vessel diameter in mm; SB %DS [%] — SB percentage diameter stenosis before stenting; SB %DS [%], post stenting — SB percentage diameter stenosis immediately after stent implantation in MV; SB %DS [%], final — final SB percentage diameter stenosis, after PCI completion; SYNTAX score — SYNergy between PCI with TAXus and cardiac surgery; FFR — fractional flow reserve

all calculated parameters for area stenosis after stenting in comparison with area stenosis before stenting: ASc initial vs. ASc poststenting — 93% ± ± 7% vs. 81% ± 29%, p = 0.002; ASc initial vs. ASmld poststenting — 93% ± 7% vs. 77% ± ± 24%, p < 0.001; ASc initial vs. ASds poststenting — 93% ± 7% vs. 56% ± 28%, p < 0.001. These imply a significant decrease in area stenosis after stenting, which is in contrast with an increase in diameter stenosis after stenting from 52% ± 24% before stenting implantation vs. 67% ± 27% after stenting (Table 2).

The correlation coefficients for the entire group with FFR values after stent implantation were: r = –0.326, p = 0.025 for ASc; r = –0.416, p = 0.004 for ASds; r = –0.511, p < 0.001 for ASmld. Interestingly, when analyzed separately, there was no significant correlation in the group with SB predilatation between FFR and calculated area stenosis by any method. In contrast, there was a significant correlation between FFR after stenting and SB ostial area stenosis in the group without SB predilatation — with the highest correlation between ASmld (r = –0.495, p = 0.006) and non-significant with ASc (r = –0.302, p = 0.099). In general, the area stenosis was significantly larger when estimated by the circle formula, than with the ellipse formula — ASc vs. ASds with 25% ± 13%, p < 0.001, ASc vs. ASmld with 9% ± 10%, p < 0.001. The differences were also significant in groups with and without SB predilatation.

When compared in groups with (n = 24, 49%) and without SB FFR ≤ 0.80, there was no significant difference in calculated circular shape ostial areas stenosis, ASc (FFR ≤ 0.80 vs. FFR > 0.80 — 94% ± 8% vs. 82% ± 25%, p = 0.098), but both calculated elliptical area stenoses were significantly different — ASmld (FFR ≤ 0.80 vs. FFR > 0.80: 88% ± 9% vs. 76% ± 13%, p = 0.008) and ASds (FFR ≤ 0.80 vs. FFR > 0.80: 68% ± 20% vs. 52% ± ± 23%, p = 0.033). On receiver-operating curve (ROC) analysis a cut-off value for identification of FFR ≤ 0.80 was found — for ASmld > 83%, ASds > 62%, ASc > 93%, with corresponding sensitivity analysis presented in Table 3.

Table 3. Sensitivity analysis of different calculated area stenoses for prediction of poststenting fractional flow reserve (FFR) ≤ 0.80.

Area stenosis	Area under the curve	P	Cut-off value for area stenosis predicting FFR ≤ 0.80 [%]	Sensitivity [%]	Specificity [%]	PPV [%]	NPV [%]	Accuracy [%]
AS MLD base — Ramanujan	0.830	< 0.001	> 83%	86%	73%	75%	84%	80%
AS SB RVD — Ramanujan	0.756	0.011	> 62%	73%	65%	67%	71%	69%
AS circular shape MLD after stenting	0.737	0.017	> 93%	73%	65%	67%	71%	69%

MLD — minimal lumen diameter; NPV — negative predictive value; PPV — positive predictive value; RVD — reference vessel diameter; SB — side branch

The ostial eccentricity (for ASmld 5.06 ± 4.66 vs. 2.89 ± 1.43, for FFR ≤ 0.80 vs. FFR > 0.80 accordingly, p = 0.093) despite being numerically higher in the group with lower FFR, and was not statistically different. The last observation suggests, that lower FFR values are associated with greatest ostial elliptic deformations, probably in cooperation with carina displacement. Comparing further, the four groups depended on FFR changes which were (< or > 0.80), as described above — negative FFR before and after stenting (group 0), newly appearing significant SB FFR < 0.80 (group 1), those with significant SB FFR before and after stenting (group 2) and finally patients with initially significant SB FFR, but non-significant after stenting (group 3). The analysis of variance revealed statistically significant differences between groups (ANOVA, p = 0.001 for ASmld, p = 0.043 for ASds, p = 0.375 for ASc). The Bonferroni correction post-hoc multiple comparison test demonstrated highly significant differences between groups 2 and 0 for ASmld (92% ± 7% vs. 68% ± 23%, p = 0.001) and borderline differences between groups 1 and 0 for ASmld (87% ± 12% vs. 68% ± ± 23%, p = 0.050). This suggests a pattern of change in FFR values (i.e., change in ostial area stenosis) regardless of its absolute values may influence FFR values after stenting.

On univariate regression analysis, significant associations of SBFFR ≤ 0.80 after stenting MV were: history of ST-segment elevation myocardial infarction in the past, presence of carotid artery disease, SYNTAX score, basic systolic blood pressure at the beginning of the procedure, stent diameter, SB predilatation, SB percentage diameter stenosis before and after stenting, minimal lumen diameter at SB ostium at baseline and after stenting, ASmld, ASds, ASc. A ROC analysis was performed to identify cut-off values for identification of FFR less than 0.80 about area stenosis calculated values (Table 3). The ASmld > 83%, ASds > 62% and ASc > 93% were also significantly associated with cut-off FFR on univariate regression analysis. On multivariate logistic regression analysis ASmld > 83%, but neither circular area stenosis values nor continuous parameter was independently associated with FFR ≤ 0.80 (OR 7.143, CI 1.006–50.000; Negelkerke R square 0.477, p = 0.002, Hosmer and Lemeshov p = 0.427).

Discussion

Over a decade ago, the deformation of the circular opening before stenting to elliptical opening

after stenting as a mechanism for SB compromise based on theoretical assumptions and observations from phantom elastic models of coronary bifurcations was proposed [2, 3]. In recent years, these theoretical and experimental observations were confirmed in optical coherence tomography imaging of coronary bifurcations after stenting MV [5, 6]. The current study provides a quantitative basis for area stenosis calculation, based on angiography data. The formulas used were adopted from the literature [8–15] and constrained based on constant vessel circumference assumption. A formula from Ramanujan was used [8, 9, 13] which provides values closest to a mean from all other formulas.

The area stenosis calculated based on elliptical assumptions provides much more physiological ostial area stenosis in better agreement with experimental observation on flow limitations caused from stenosis [16, 17]. This is more important in less severe stenoses (< 70% area stenosis), where differences in areas are larger, while in more severe stenosis (> 70% area stenosis) the shape of the ostium does not seem to be so important and the values of area stenosis are more circular, no matter which formula is used. It should be noted that the present calculations are based on the assumption of the ability of ostium of SB to deform freely, quantitatively expressed by a stretching coefficient k. In reality, the presence of plaque with fibrous content and calcium can preclude these deformations [18].

To provide a better association between area stenosis and functional stenosis, calculated data was compared with experimental data for functional stenosis (i.e., FFR). The area stenosis in patients from the FIESTA study was calculated using formulas based on elliptical shape correlates better with parameter for functional stenosis, such as FFR, than the area stenosis calculated based on circle form of the ostium ($r = –0.326$ for ASc; $r = –0.416$ for ASds; $r = –0.511$ for ASmld). Moreover, the area stenosis based on elliptical shape (ASmld) has significantly better accuracy for identification of significant FFR after stenting, than area stenosis, calculated based on circular ostial shape. For the first time, a practical form for calculation of ellipse type of opening was provided herein, based only on angiographic data. These formulas can be implemented in future with software programs for automatic analysis. It can be speculated that elliptical ostial shaping is a final common pathway that occurs at the ostium after main vessel stenting. Elliptical stretch and deformation could occur and can explain side branch ostial stenosis (even high-grade) at 90° occurring branches from the main vessel, where carina shifting is theoretically impossible.

In accordance with the assumptions for initial circular side branch minimal lumen diameter, which transforms to ellipse, are data from the literature, demonstrating that almost 90% of bifurcations have circular ostia [5, 6]. Why the ASmld formula performs best in prediction of significant FFR after main vessel stenting? The most plausible reason is that it relays on three different parameters (side branch MLD before and after stenting and SB reference diameter), while ASds and ASc relay only on two parameters — SBMLD after stenting and SBRVD. Thus, ASmld incorporates the basic information of lesion flow limiting capacity, not only information obtained after stenting.

The areas at the ostium calculated in the present study are considerably smaller than those reported in the literature [5, 6, 19, 20]. This may be explained by differences in imaging methods (angiography, optical coherence tomography, or intravascular ultrasound). Optical coherence tomography visualizes the shape and size of SB, while the minimum ostial area (calculated based on angiographic data) can appear at a distance from the SB opening, because of invagination of the side vessel wall — see Figure 1 from reference no. 6. One possible explanation is a difference in patient populations — the present group has larger SB reference diameters than those previously reported (2.51 mm vs. 2.0–2.2 mm in other studies). All our patients have significant MV FFR values before interventions and practically half of the current patients had functionally true bifurcations. This percentage is larger than typically reported (around 30% or less).

Limitations of the study

The present study has several limitations. First, it did not consider the other two mechanisms of SB compromise — carina displacement and plaque shift. The theoretical data and cross-calculated parameters assuming elliptical ostial deformation of SB ostium after stenting however, correlate very well with the parameter of physiological severity, namely FFR. It must be pointed out, that carina displacement is one of the suggested mechanisms causing ellipse formation at SB ostium. This may explain the good correlations observed in the present study. Further research is needed to implement carina and plaque shifts in the model to better predict the observed changes. Second, only angiographic analysis and measure-

ments of vessel sizes was performed. This is subject to a significant inaccuracy and variation. Three-dimensional optical coherence tomography imaging might have offered better visualization of the elliptic deformation of the SB ostium. However, such elliptic deformation has already been demonstrated by others [5, 6]. Third, the group of patients is relatively small. Given that half of angiographically significant coronary bifurcation stenosis are functionally insignificant by means of FFR values, however, it becomes rather impractical to find many appropriate patients for such a study [21].

Conclusions

The elliptical ostial transformation of side branches after MV stenting of coronary bifurcation is a possible mechanism for SB compromise. The ostial area stenosis, calculated based on this assumption correlates better with the physiological parameter of lesion severity, i.e. FFR, compared to area stenosis calculated based on the traditional circular formula.

Conflict of interest: None declared

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Reproducibility of optical coherence tomography in vein grafts used for coronary revascularization

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Abstract

Background: *Optical coherence tomography (OCT) is a high-resolution imaging modality able to provide near-histological images of vessel walls making it possible to distinguish intima and media layers of the vessel wall separately. The use of this imaging technique is increasing while data on the variability and reliability is lacking. The aim of this study was to investigate the reproducibility of frequency-domain OCT in vein grafts used for coronary revascularization.*

Methods: *Five pullbacks were analyzed by the same analyst with a 1-month delay (intraobserver) and by two different analysts (interobserver). Five pairs of pullbacks from the same catheters and vein graft were also analyzed (inter pullback).*

Results: *Optical coherence tomography showed low variability in intra- and interobserver analysis with relative differences of mean media and intima thicknesses and areas of less than 5% for most parameters. Relative differences of the same parameters in the inter pullback analysis were in the 5–15% range. Intra- and interobserver reliability was excellent (intraclass correlation coefficient [ICC] > 0.90) for intima thickness and intima, media and intima-media area measurements. Inter pullback reliability was good (ICC: 0.75–0.90) for intima and intima-media area measurements, and moderate to good for mean intima thickness measurements (ICC: 0.79; 0.7338–0.8284).*

Conclusions: *Optical coherence tomography provides good reproducibility for the measurements of parameters relevant for the development of atherosclerosis in vein grafts.*

Clinical trial registration: *ID NCT01834846.* (Cardiol J 2020; 27, 5: 518–523)

Key words: coronary artery disease, saphenous vein graft, intimal hyperplasia

Introduction

Frequency-domain optical coherence tomography (FD-OCT) is a high-resolution intravascular imaging modality that generates near-histological quality in-vivo images of the coronary vessel wall [1]. OCT is being adopted worldwide as an important part of clinical decision-making as well as a promising research tool [2]. Historically, intravascular ultrasound (IVUS) has been the gold

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standard for evaluating the development of intimal hyperplasia in coronary arteries and vein grafts [3–5]. However, IVUS is not able to distinguish between the intima and the media layers of the vessel wall [6]. OCT provides superior resolution by using near-infrared light instead of ultrasound for image acquisition. This provides a more accurate estimate of morphological properties such as lumen diameter [7] and enables researchers to differentiate between the different layers of the vessel wall.

Previous studies have shown excellent intraobserver, interobserver and inter pullback reproducibility for quantitative OCT measurements of lumen diameters and intimal hyperplasia thickness as well as morphometric stent parameters in native coronary arteries [8–10]. Clinical trials using intimal hyperplasia measured with OCT as a marker of development of atherosclerosis in vein grafts are published [11–14]. However, studies investigating the reproducibility of similar parameters in vein grafts used for coronary artery bypass grafting (CABG) are lacking. Different histological morphology and increased diameters in saphenous vein grafts (SVG) compared to native coronary arteries could influence reproducibility of OCT.

Methods

Study population

This paper reports reproducibility data from OCT images obtained from patients undergoing CABG using SVG as a conduit for revascularization. The patients were included in a single center randomized trial on SVG harvesting [15]. The patients were examined with OCT 6 months following surgery. The study is registered in Clinicaltrial.org (ID NCT01834846). The study complied with the Consolidated Standards of Reporting Trials (CONSORT) criteria.

Image acquisition

Optical coherence tomography pullbacks were obtained using commercially available, frequency-domain system (ILUMIEN™ PCI Optimization System, OCT Intravascular Imaging System; St. Jude Medical, St. Paul, MN, USA). A 2.7 F OCT imaging catheter (Dragonfly; LightLab Imaging, Inc.) was advanced into the vein graft after administration of nitroglycerin (200 μg) into the graft. An integrated automated pullback device was used with a speed of 20 mm/s. The maximal pullback length allowed by the system was 55 mm. The blood was cleared by injection of isoosmolar contrast (Iohexol 350 mgI/L Omnipaque, GE Healthcare, Dublin, Ireland) at 37°C with an injection pump (ACIST CVi System [ACIST Medical Systems Inc., Eden Prairie, MN, USA]) through the guiding catheter during image acquisition. The size of the vein graft was considered from the angiography and subsequently contrast flow rate and contrast volume given by the Acist system. If the first pullback did not give acceptable pictures, flow rate and volume was adjusted. These parameters were identical between pairs of pullbacks undergoing intra-catheter reproducibility analysis.

All images were digitally stored in the FD-OCT system console and on DVD for later off-line analysis.

Imaging analysis

Optical coherence tomography analyses were performed at an independent core laboratory (KCRI, Krakow, Poland). OCT pullbacks were analysed using OCT — Ilumien Optis, Offline Review Workstation (St. Jude Medical, USA).

A single, individual analysis comprised of qualitative and quantitative assessment for each graft of interest. OCT analysis was performed according to current consensus standard [16, 17], which focused on measuring thicknesses, areas for intima and media separately. Lumen area was automatically detected and contoured by the software and was manually corrected by the analyst, if necessary. The intima and media contours were delineated for every 1 mm frame in the region of interest. Frames without clear delineated intima-media border at the entire circumference were excluded from analysis. Intima thickness was defined as the thickness of the high backscattering or signal rich area inside the internal elastic lamina (IEL) in each frame of the pullback. Media thickness was calculated as the mean thickness of the low backscattering area between the IEL and external elastic lamina (EEL) (Fig. 1). Figures 2 and 3 show an example of the maximum difference in media thickness measurements between two separate analyses performed by the same analyst (Fig. 2) and two independent analysts (Fig. 3). For the inter pullback analysis, matching of the frames between the pullbacks were initiated by identifying one corresponding frame visible on both recordings. After finding the corresponding frame, analysis was performed every 1 mm from this frame, assuring that it covered exactly the same region of interest (the same vessel fragment) as with the previous analysis.

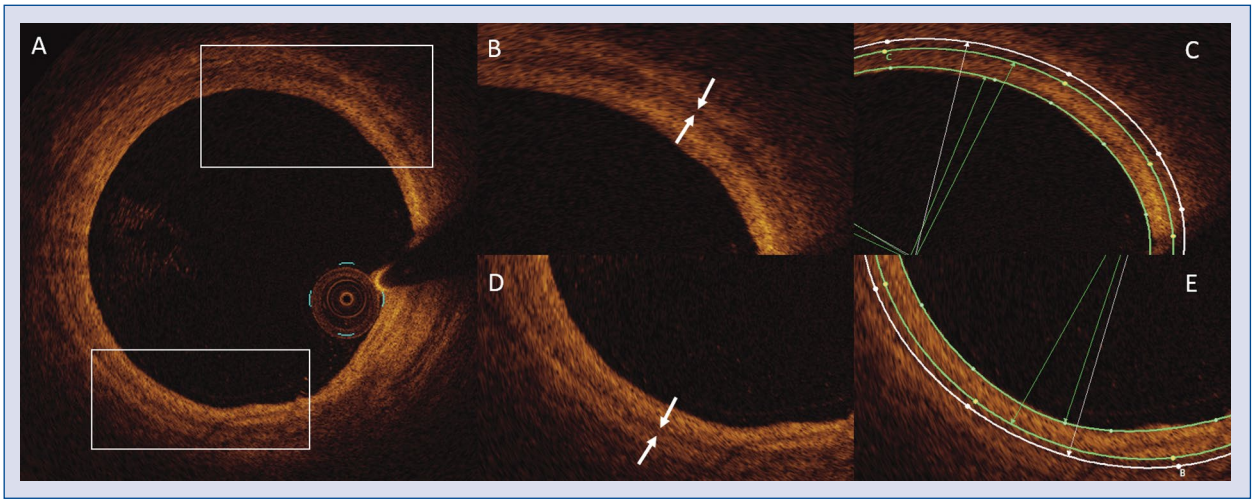

Figure 1. A. Vessel cross-sectional view; **B, D.** Magnified parts with media (white arrows); **C, E.** Corresponding frames with lumen (inner green contour), internal elastic lamina (middle green contour) and external elastic lamina (outer white contour) contours. The area between the lumen and the internal elastic lamina is the intima area, whereas the area between the internal and external lamina is the media area.

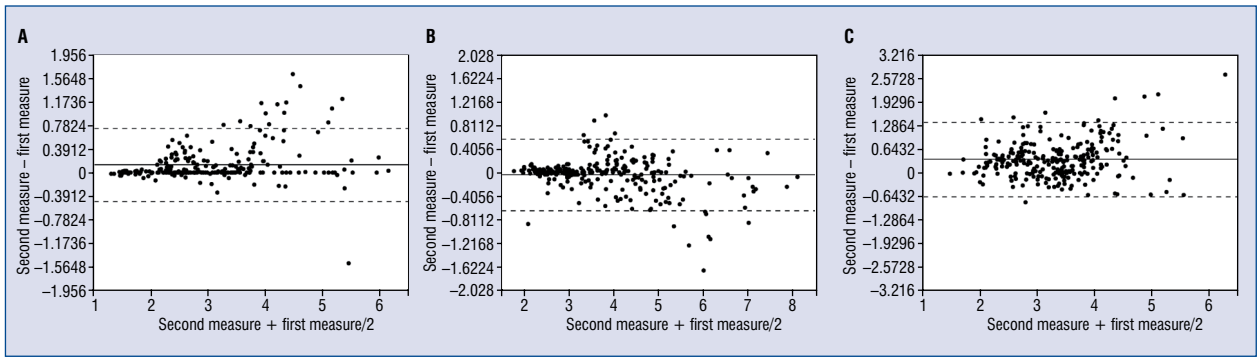

Figure 2. A. Bland-Altman plots of intraobserver measurements of intima area; **B.** Bland-Altman plots of interobserver measurements of intima area; **C.** Bland-Altman plots of inter pullback measurements of intima area.

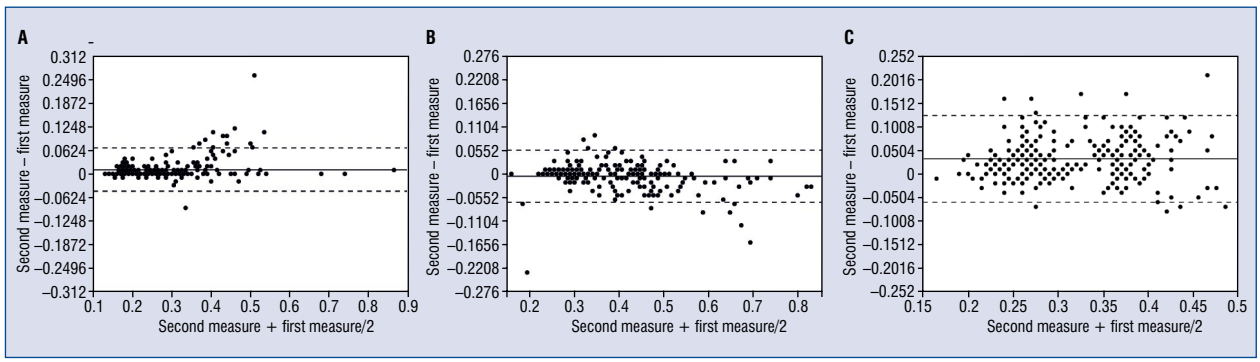

Figure 3. A. Bland-Altman plots of intraobserver measurements of average intima thickness; **B.** Bland-Altman plots of interobserver measurements of average intima thickness; **C.** Bland-Altman plots of inter pullback measurements of average intima thickness.

Statistical analysis

Five pullbacks with a total of 243 frames were analyzed two times with a 1 month delay on the same software under the same conditions by the same analyst (intra-analysis). Five pullbacks with a total of 258 frames were analyzed correspondingly by two different analysts (inter-analysis). Different frames were analyzed in the interobserver and the intraobserver analysis. Five pullbacks with a total of 258 corresponding frames were analyzed by the same analyst on two different pullbacks obtained from the same OCT catheter and vein graft (inter pullback analysis).

Results of the first and the second measurements were presented as a mean with 95% confidence interval (CI) and as median with the first and the third quartiles. Normality of distribution was assessed using the Shapiro-Wilk test. Discrepancies between the first and the second analysis were calculated as absolute and relative differences and were presented as means with 95% CIs. Intraclass correlations were calculated as the main measure of agreement along with the graphical representation as Bland-Altman plots. The intraclass correlation coefficients (ICCs) were calculated based on two-way random effect models [18, 19].

Results

Results of intraobserver, interobserver and inter pullback variability and reliability analysis are presented in Tables 1, 2 and 3, respectively. Bland-Altman plots of interobserver, intraobserver and inter pullback intima area and intima thickness measurements are demonstrated in Figures 2 and 3. The variability of the measurements in the intra- and interobserver analysis was low, the relative differences of mean media and intima thicknesses and areas were of less than 5% for most parameters. Relative differences of the same parameters in the inter pullback analysis were in the 5–15% range. There were excellent intra- and inter-observer reliability (ICC: 0.90–1.00) for intima and intima-media area as well as diameter measurements. There was good inter pullback reliability on intima and intima-media area measurements (ICC: 0.75–0.90), whereas the mean intima thickness measurements showed moderate to good reliability. The reliability of media thickness measurements was in general poorer in all groups, this is likely due to the absolute thickness being relatively small compared to the other measurements.

Discussion

Reproducibility of measurements relating to intimal hyperplasia was satisfactory for all variables in the study. The results revealed that albeit satisfactory, the inter pullback reproducibility was inferior to the intra- and interobserver reproducibility. There may be different reasons for this. Pullbacks in the inter pullback analysis were matched frame by frame, however 1 mm on one pullback does not necessarily correspond to 1 mm on the other pullback due to cardiac motion during the recording process. Thus, it is possible that the matching of each frame on the pullback did not correspond 100% with the the previous frames. The absolute difference in small measurements from one frame to the next were small, however relative difference was large, corresponding to a lower ICC than what may be expected.

The data reported here demonstrates the morphological properties of each frame in the vein grafts. Studies reporting vein wall properties are likely to report mean values for segments of vein grafts, not individual frames. This should provide even better inter pullback reliability than that of individual frames, as the problem of matching frames is largely negated. Vein grafts are in general quite large compared to coronary arteries. FD-OCT relies on adequate flushing of blood to achieve acceptable image acquisition. The present experience is that the contrast flow and volume during the pullback must be sufficiently large to provide adequate vein graft flushing during pullback. To obtain this an injection pump for contrast was necessary and several patients received multiple pullbacks of their vein grafts before satisfactory images were acquired. The combination of large lumen, a thickening intima layer and the limited penetration depth associated with OCT are the main limiting factors when visualizing the vein wall.

Reproducibility of longitudinal measurements was not investigated in this study, due to the lack of landmarks for longitudinal measurements. The vein grafts in this study were investigated at 6 months, and as expected there was no evidence of atherosclerotic disease or lesions other than diffuse intimal hyperplasia. The aim of the study was to assess cross sectional vessel wall characteristics. Longitudinal reproducibility should be investigated in vein grafts at a later time point, focusing on atherosclerotic lesion length or stent parameters in vein grafts after undergoing percutaneous coronary intervention.

Table 1. Intraobserver reliability.

	First measure		Second measure		Mean difference [CI]	Mean relative difference [CI]	ICC [CI]
	Mean [CI]	Median [Q1–Q3]	Mean [CI]	Median [Q1–Q3]			
Intima thickness mean	0.27 [0.25–0.28]	0.24 [0.18–0.33]	0.28 [0.26–0.29]	0.25 [0.18–0.33]	–0.01 [–0.01 to –0.01]	3.13% [2.29–3.98%]	0.98 [0.97–0.98]
Media thickness mean	0.08 [0.08–0.09]	0.08 [0.07–0.10]	0.09 [0.08–0.09]	0.09 [0.07–0.11]	–0.00 [–0.01 to –0.00]	4.71% [2.99–6.44%]	0.79 [0.74–0.83]
Intima-media complex area	4.04 [3.90–4.17]	3.98 [3.44–4.61]	4.23 [4.08–4.39]	4.15 [3.50–4.82]	–0.20 [–0.25 to –0.15]	3.96% [3.13–4.80%]	0.95 [0.93–0.96]
Intima area	2.98 [2.86–3.10]	2.75 [2.31–3.55]	3.11 [2.97–3.24]	2.83 [2.40–3.71]	–0.13 [–0.16 to –0.09]	3.36% [2.49–4.24%]	0.96 [0.95–0.97]
Media area	1.06 [1.01–1.10]	0.98 [0.77–1.39]	1.13 [1.08–1.17]	1.04 [0.83–1.40]	–0.07 [–0.09 to –0.05]	5.86% [4.12–7.59%]	0.88 [0.85–0.91]

CI — confidence interval; ICC — intraclass correlation coefficient

Table 2. Interobserver reliability.

	First measure		Second measure		Mean difference [CI]	Mean relative difference [CI]	ICC [CI]
	Mean [CI]	Median [Q1–Q3]	Mean [CI]	Median [Q1–Q3]			
Intima thickness mean	0.38 [0.36–0.39]	0.33 [0.28–0.44]	0.37 [0.36–0.39]	0.33 [0.28–0.44]	0.01 [0.00–0.01]	–0.86% [–1.78–0.07%]	0.97 [0.96–0.98]
Media thickness mean	0.08 [0.07–0.08]	0.07 [0.06–0.08]	0.08 [0.08–0.08]	0.08 [0.07–0.08]	–0.00 [–0.00 to –0.00]	3.38% [1.90–4.87%]	0.78 [0.73–0.83]
Intima-media complex area	4.77 [4.60–4.94]	4.63 [3.60–5.49]	4.75 [4.59–4.92]	4.74 [3.61–5.61]	0.02 [–0.02–0.06]	–0.18% [–0.83–0.46%]	0.97 [0.97–0.98]
Intima area	3.87 [3.70–4.03]	3.61 [2.78–4.69]	3.82 [3.67–3.97]	3.70 [2.82–4.57]	0.05 [0.01–0.08]	–0.64% [–1.44–0.17%]	0.97 [0.96–0.98]
Media area	0.91 [0.87–0.94]	0.82 [0.71–1.03]	0.93 [0.90–0.97]	0.88 [0.75–1.03]	–0.03 [–0.04 to –0.01]	3.04% [1.67–4.42%]	0.89 [0.87–0.92]

CI — confidence interval; ICC — intraclass correlation coefficient

Table 3. Inter pullback reliability.

	First measure		Second measure		Mean difference [CI]	Mean relative difference [CI]	ICC [CI]
	Mean [CI]	Median [Q1–Q3]	Mean [CI]	Median [Q1–Q3]			
Intima thickness mean	0.30 [0.29–0.31]	0.29 [0.24–0.35]	0.33 [0.32–0.34]	0.32 [0.27–0.39]	–0.03 [–0.04 to 0.03]	9.23% [7.72–10.74%]	0.79 [0.73–0.83]
Media thickness mean	0.08 [0.07–0.08]	0.07 [0.06–0.10]	0.08 [0.08–0.09]	0.08 [0.07–0.10]	–0.01 [–0.01 to 0.01]	10.46% [8.09–12.83%]	0.62 [0.53–0.69]
Intima-media complex area	4.01 [3.90–4.12]	3.96 [3.22–4.73]	4.48 [4.36–4.60]	4.35 [3.72–5.15]	–0.47 [–0.53 to 0.40]	9.99% [8.71–11.27%]	0.85 [0.81–0.88]
Intima area	3.12 [3.02–3.21]	3.14 [2.48–3.61]	3.47 [3.36–3.58]	3.40 [2.88–4.00]	–0.35 [–0.42 to 0.29]	9.54% [8.00–11.07%]	0.81 [0.76–0.84]
Media area	0.90 [0.85–0.94]	0.79 [0.60–1.18]	1.01 [0.97–1.04]	0.94 [0.76–1.23]	–0.11 [–0.14 to 0.09]	12.07% [9.74–14.39%]	0.79 [0.74–0.83]

CI — confidence interval; ICC — intraclass correlation coefficient

Limitations of the study

The reliability of results presented in this paper are based on a limited number of pullbacks and larger studies are warranted. Studies comparing OCT and IVUS to histological specimen would be ideal in providing assistance to determine a gold standard for imaging morphological development of vein grafts following CABG.

Conclusions

Optical coherence tomography provides a reliable intraobserver, interobserver and inter pullback assessment of vein graft intimal hyperplasia and other relevant parameters for assessing vein graft morphology. Concluded herein, OCT is a suitable tool for assessing early markers of vein graft disease.

Conflict of interest: None declared

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Comparison of Figulla Flex® and Amplatzer™ devices for atrial septal defect closure: A meta-analysis

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Abstract

Background: *Atrial septal defect (ASD) is one of the most common congenital heart diseases. Percutaneous closure is the preferred treatment, but certain complications remain a concern. The most common devices are AMPLATZER™ (ASO) (St. Jude Medical, St. Paul, MN, USA) and Figulla Flex® septal occluders (FSO) (Occlutech GmbH, Jena, Germany). The present study aimed to assess main differences in outcomes.*

Methods: *A systematic search in Pubmed and Google scholarship was performed by two independent reviewers for any study comparing ASO and FSO. Searched terms were "Figulla", "Amplatzer", and "atrial septal defect". A random-effects model was used.*

Results: *A total of 11 studies including 1770 patients (897 ASO; 873 FSO) were gathered. Baseline clinical and echocardiographic characteristics were comparable although septal aneurysm was more often reported in patients treated with ASO (32% vs. 25%; p = 0.061). Success rate (94% vs. 95%; OR: 0.81; 95% CI: 0.38–1.71; p = 0.58) and peri-procedural complications were comparable. Procedures were shorter, requiring less fluoroscopy time with an FSO device (OR: 0.59; 95% CI: 0.20–0.97; p = 0.003). Although the global rate of complications in long-term was similar, the ASO device was associated with a higher rate of supraventricular arrhythmias (14.7% vs. 7.8%, p = 0.009).*

Conclusions: *Percutaneous closure of ASD is a safe and effective, irrespective of the type of device. No differences exist regarding procedural success between the ASO and FSO devices but the last was associated to shorter procedure time, less radiation, and lower rate of supraventricular arrhythmias in follow-up. Late cardiac perforation did not occur and death in the follow-up was exceptional.* (Cardiol J 2020; 27, 5: 524–532)

Key words: Figulla, Amplatzer, atrial septal defect

Introduction

Atrial septal defect (ASD) is one of the most common congenital cardiac diseases representing up to 8% of them. As a main type, the therapeutic management of *ostium secundum* ASD has quickly evolved from surgery to percutaneous closure despite the low mortality rate (< 1%) of surgical repair. This can be explained by the good results of percutaneous closure through a less invasive procedure. Since first percutaneous closure of an ASD was performed more than four decades ago [1–3], and different devices have been proved to be safe and effective. In the last decade, the most commonly used ASD closure devices include the Amplatzer Septal Occluder (ASO) (Abbott Vascular®,

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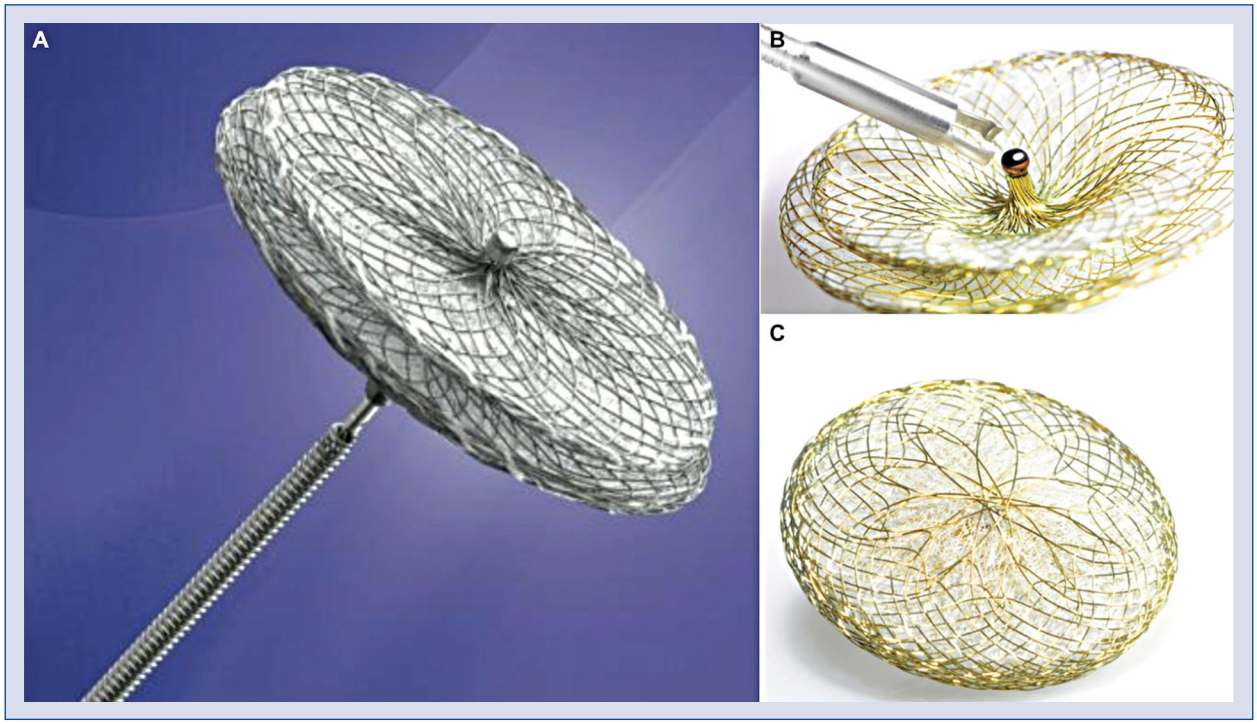

Figure 1. Amplatzer septal occluder (**A**) and Figulla Flex II (**B**, **C**) showing main differential features of Figulla Flex including the lack of screw attachment (replaced by a ball, **B**) and the smooth left atrial disc (**C**).

California, USA) and the more recent Figulla Flex septal occluder (FSO) (Occlutech® GmbH, Jena, Germany). The last has been developed in order to minimize complications while maintaining efficacy. However, comparisons of this device with those representing a broader experience is limited to a short series and potential advantages of the newer devices remain unproven. This is of major interest given the current investigations focused on bioresorbable closure devices that will require comparison with quality standards.

The ASO (Fig. 1A) is composed of a nitinol metal wire mesh that holds two self-expanding discs, and can be steadily deployed and recaptured [4, 5]. Dacron patches with a pro-coagulant material have been placed within the mesh in order to promote thrombosis and endothelialization [3–5]. Concerns with this device include those related to the procedure as embolization or residual shunt, and the rare but worrisome risk of tissular erosion/ /perforation in the long term. The newer Figulla Flex device (Fig. 1B, C) aims to diminish the risk of these complications through a less heavy mesh theoretically providing greater flexibility with less aggression to the tissues, and its deliverability in mainly larger defects is simplified. Also, the lack of a micro-screw potentially allows a smooth delivery and decreases the risk of clot formation [1, 4]. As was said, large prospective randomized studies have not been performed to explore these aspects. Hence, the aim herein was to compare the FSO and ASO devices in current cohorts through a meta-analysis in order to determine rates of success, as well as short- and long-term complications which each system.

Methods

Literature search strategy

A systematic review of all published research in PubMed and Google-Scholar databases between February/2009 and February/2018 regarding percutaneous closure of ASDs was independently performed by two authors (AA and IJAS). The following terms were used: "Figulla", "Amplatzer", and "atrial septal defect" (Fig. 2). Only full English peer-reviewed articles were selected and editorials or expert opinions were ruled out. Discrepancies between reviewers were resolved by discussion, and a consensus was reached.

Eligibility criteria

Eligible studies were considered those directly comparing outcomes of patients receiving either ASO

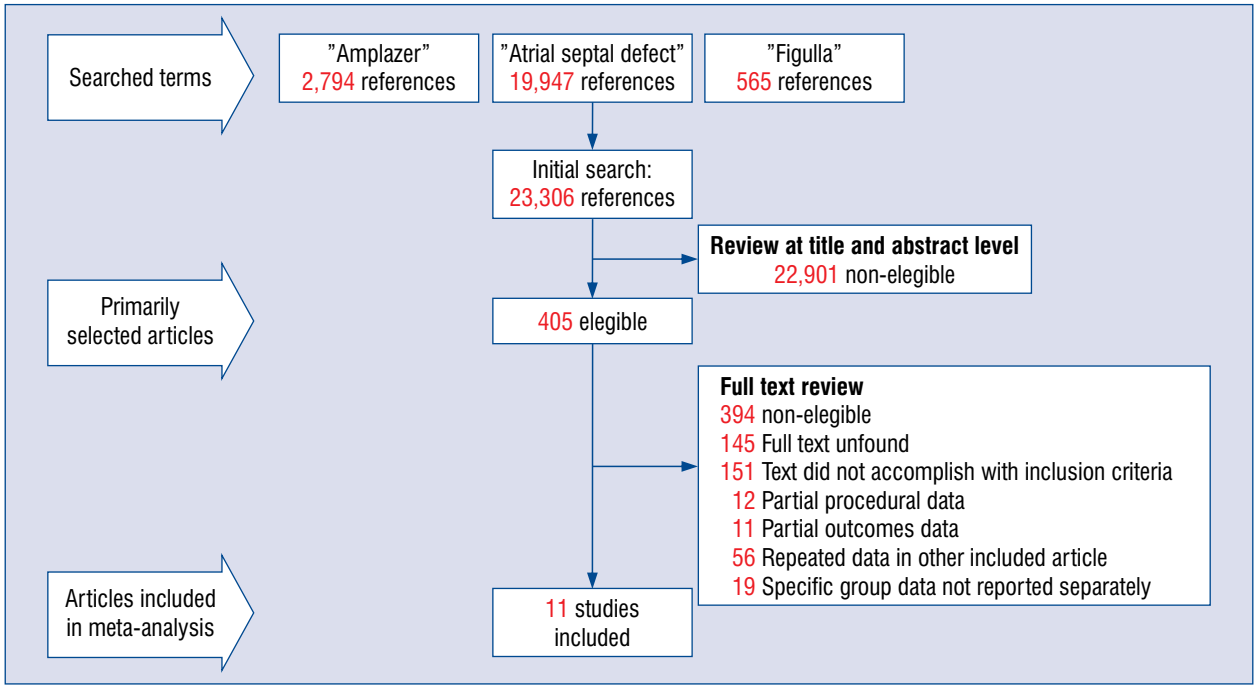

Figure 2. Flow chart showing search results and selection of the studies included in the meta-analysis.

or FSO closure devices and reporting peri-procedural and long-term outcomes. Events were entered as zeros in the tables for those studies that reported no complications during the follow-up period.

Main outcomes

Primary outcomes were procedural success, peri-procedural, and long-term complications. The last included cardiac perforation, cardiac death (including those of unknown origin), neurological events, and thrombus formation at any time point. Long-term was considered to be at least 6 months of follow-up.

Statistical analysis

Qualitative variables are expressed as an absolute frequency and percentage. Continuous variables are expressed as mean ± standard deviation unless otherwise specified. In order to compare demographic variables and risk factors between groups, the χ^2 or the Fisher test were used for categorical variables and the Student-t test for continuous variables in cases where it was required.

Potential publication bias was assessed by using a funnel plot. As a measure of the combined effect for the studies included, the odds ratio (OR) was estimated, valid for prospective and retrospective studies. The confidence interval (CI) was at 95%, as well as its statistical significance. The homogeneity between studies was contrasted by the Q_H statistic. In regard to the low sensitivity of this test, $p < 0.10$ values were considered as significant. To overcome this limitation in some way, the I^2 statistic was estimated as well, which measures the proportion of the total variation of the studies explained by the heterogeneity and its 95% CI. A random effects model was used for those cases in which the I^2 statistic was greater than 50% and the model of fixed effects for opposite cases. A random effects model was used for all outcomes to obtain a loose estimate due to the inclusion of prospective and retrospective studies.

All p values were two sided. All analyses were conducted using the statistical software Review Manager 5.3.

Results

Patient distribution and baseline characteristics.

A total of 1,827 patients from 11 different studies (**Suppl. Table 1**) [6–16] underwent percutaneous ASD closure, with ASO (n = 897, 49.1%) or FSO (n = 873, 47.8%). Additionally, 57 patients (3.1% from the global study population) were excluded from the final analyses because a different device was used.

Table 1. Reported baseline characteristics, procedural and follow-up outcomes.

Variables	Global study population N = 1,827	Amplatzer N = 897/1,770 (50.7%)	Figulla N = 873/1,770 (49.3%)	P
Baseline characteristics				
Females	663/1,099 (60%)	350 (62%)	313 (58%)	0.154
Age [years]	45.48 ± 10.39	44.08 ± 11.48	47.02 ± 9.08	**< 0.001**
Hypertension	149/634 (24%)	85/297 (29%)	64/337 (19%)	**0.004**
Diabetes	15/634 (24%)	9/297 (3%)	6/337 (2%)	0.301
Dyslipemia	144/493 (29%)	66/225 (29%)	78/268 (29%)	0.956
Smoking	72/493 (15%)	44/225 (20%)	28/268 (10%)	**0.004**
TIA	411/744 (55%)	193/347 (56%)	218/397 (55%)	0.846
Stroke	218/634 (34%)	102/297 (34%)	116/337 (34%)	0.983
Recurrent ischemic or embolic events	222/634 (35%)	105/297 (35%)	117/337 (35%)	0.867
Thrombophilia	84/594 (14%)	39/277 (14%)	45/317 (14%)	0.995
Atrial septal aneurysm	186/657 (28%)	96/301 (32%)	90/356 (25%)	0.061
NYHA III–IV	10/149 (7%)	5/72 (7%)	5/77 (6%)	0.999
Procedural outcomes				
Procedural success	788/809 (97.4%)	435/446 (98%)	353/363 (97%)	0.8
Procedural time [min]	40.59 ± 25.25	41.82 ± 22.54	39.24 ± 27.94	0.166
Fluoroscopic time [min]	11.60 ± 20.05	12.22 ± 19.42	10.91 ± 20.73	**< 0.001**
Device size [mm]	21.18 ± 4.23	21.19 ± 3.87	21.16 ± 4.65	0.37
Device embolization	9/1,683 (0.53%)	3/848 (0.4%)	6/826 (1%)	0.337
Vascular complication	9/908 (1%)	4/441 (0.9%)	5/458 (1.1%)	0.999
Residual shunt	131/1,287 (10.2%)	46/373 (12.2%)	54/386 (9%)	0.075
Stroke/TIA	1/1,770 (0.05%)	0	1/873 (0.1%)	0.999
Device thrombosis	0	0	0	0.999
Coronary embolism	1/101 (1%)	1/52 (2%)	0	0.999
Death	1/445 (0.2%)	1/445 (0.2%)	0/463	0.999
Follow up outcomes				
Death	0	0	0	–
Aortic erosion	0	0	0	–
Device fracture	0	0	0	–
Stroke/TIA	5/788 (0.6%)	2/251 (0.8%)	3/296 (1%)	0.999
Endocarditis	1/788 (0.1%)	0	1/296	0.999
Residual shunt (at 6–12 months)	70/788 (8.79%)	17/222 (7.7%)	17/160 (10.6%)	0.31
SVA and AF	60/547 (11%)	37/251 (14.7%)	23/296 (7.8%)	**0.009**
SVA	50/406 (12.3%)	30/179 (16.8%)	20/227 (8.8%)	**0.006**
AF	10/547 (1.8%)	7/251 (2.8%)	3/296 (1%)	0.198

AF — atrial fibrillation; NYHA — New York Heart Association; SVA — supraventricular arrhythmia; TIA — transient ischemic attack

Baseline characteristics of the study population are summarized in Table 1. Age and gender were similar between treatment groups with a higher proportion of women (60% vs. 40%, p = 0.154). There were no statically significant differences regarding cardiovascular risk factors, except for a higher incidence of hypertension (29% vs. 19%; p = 0.004) and smoking (20% vs. 10%; p = 0.004) in patients treated with ASO. The rate of neurovascular events was very similar across both groups. No other differences were found.

Screening protocol and peri-procedural characteristics

Prior to the percutaneous procedure, patients underwent screening with transthoracic/ /transesophageal echocardiography in all cases. Screening protocols ruled out associated neurovascular, hematological or other conditions. During the pre-procedural evaluation, the presence of atrial septal aneurysm was more often detected in patients treated with ASO (32% vs. 25%; p = 0.061).

Overall, success rate was comparable (94% for ASO vs. 95% for FSO; OR: 0.81; 95% CI: 0.38–1.71; p = 0.58) irrespective of its use for PFO or ASD, but shorter procedure and fluoroscopy times were obtained with the FSO device (OR: 0.59; 95% CI: 0.20–0.97; p = 0.003) despite similar device size (Fig. 3; **Suppl. Figs. 1, 2**). General anesthesia was the preferred strategy for both devices.

Periprocedural complications

No differences were found regarding the rate of failed closure or device embolization (0.04% vs. 0.1%, p = 0.337) but the absolute rate of residual shunt after the procedure was higher in patients treated with ASO than with FSO (12.2% vs. 9%; p = 0.075). The incidence of main complications is summarized in Table 1.

One procedural-related death due to cardiac perforation during balloon sizing was reported though the patient died 2 months later as a result of other hospitalization-related complications. Also, one transient ischemic event occurred a few minutes after ASD closure. Finally, 1 case of coronary embolism, and 2 of device thrombosis were also reported.

A pooled analysis of all procedural related complications (including cardiac perforation, device embolization, device thrombosis, severe arrhythmias, vascular complication, neurological events, and coronary embolism) was performed demonstrating the lack of statistical difference between both devices.

Follow-up outcomes.

Follow-up data were reported in all the articles. The mean follow-up for the global study population was 10.7 ± 6.9 months. Main complications within this period are summarized in Table 1. Post-procedural differences in the rate of residual shunt did not persist in the follow-up (8.5% vs. 9.3%, OR: 1.04; 95% CI: 0.60–1.79; p = 0.89) as depicted in Figure 3. However, the rate of supraventricular arrhythmia + atrial fibrillation was significantly higher after ASO (14.7%) than after FSO (7.8%, p = 0.009) in the pooled analysis. This statistical difference did not persist when a separate analysis was performed for PFO and ASD patients but a trend persisted in PFO cases and absolute values of this complication remained higher in patients harboring ASO devices (**Suppl. Table 2**).

The most frequent severe complication in long-term was recurrent neurovascular event including 3 cases of transient ischemic attack and 1 case of stroke. None who presented adhered thrombi to the device but, on the contrary, in half of them a residual shunt was present requiring surgical closure [10]. Four cases of device thrombosis were observed, one of them was noted at 12 months after the intervention, which required surgical removal [10]; the other 3 cases presenting this complication, despite continued dual antiplatelet therapy and was successfully managed with intravenous heparin and oral anticoagulation [11]. One case of infective endocarditis due to *Staphylococcus lugdunensis* was reported 3 months after device placement, had positive blood cultures but no vegetation on the device as assessed by transesophageal echocardiography, and infection resolved after antibiotic treatment [7]. None of the studies reported any death or other major complication such as aortic erosion or device fracture in follow-up.

Regarding the antithrombotic strategy 6 studies reported the use of intravenous heparin during the procedure and, afterwards, 4 studies recommended transitory dual antiplatelet therapy (acetylsalicylic acid [ASA] + clopidogrel) whereas single antiplatelet therapy with ASA was preferred in 4 more studies. Prophylaxis of endocarditis was recommended for up to 6 months.

Discussion

Percutaneous closure of *ostium secundum* ASD has become the standard care over the last decades [17–20]. Currently, alternative devices can be used in this scenario with ASO and FSO being the preferred ones. Notwithstanding this, large comparative studies of these technologies remain lacking. This meta-analysis demonstrated that, in similar populations, both devices present comparable success rates (≥ 97% for both) and also a similar rate of main procedural-related complications including imaging findings such as residual shunt (~9% at 1-year follow up) or device thrombosis. However, procedures where shorter with FSO suggesting a simpler delivery process, requiring less radiation which is a sensitive aspect in this young target

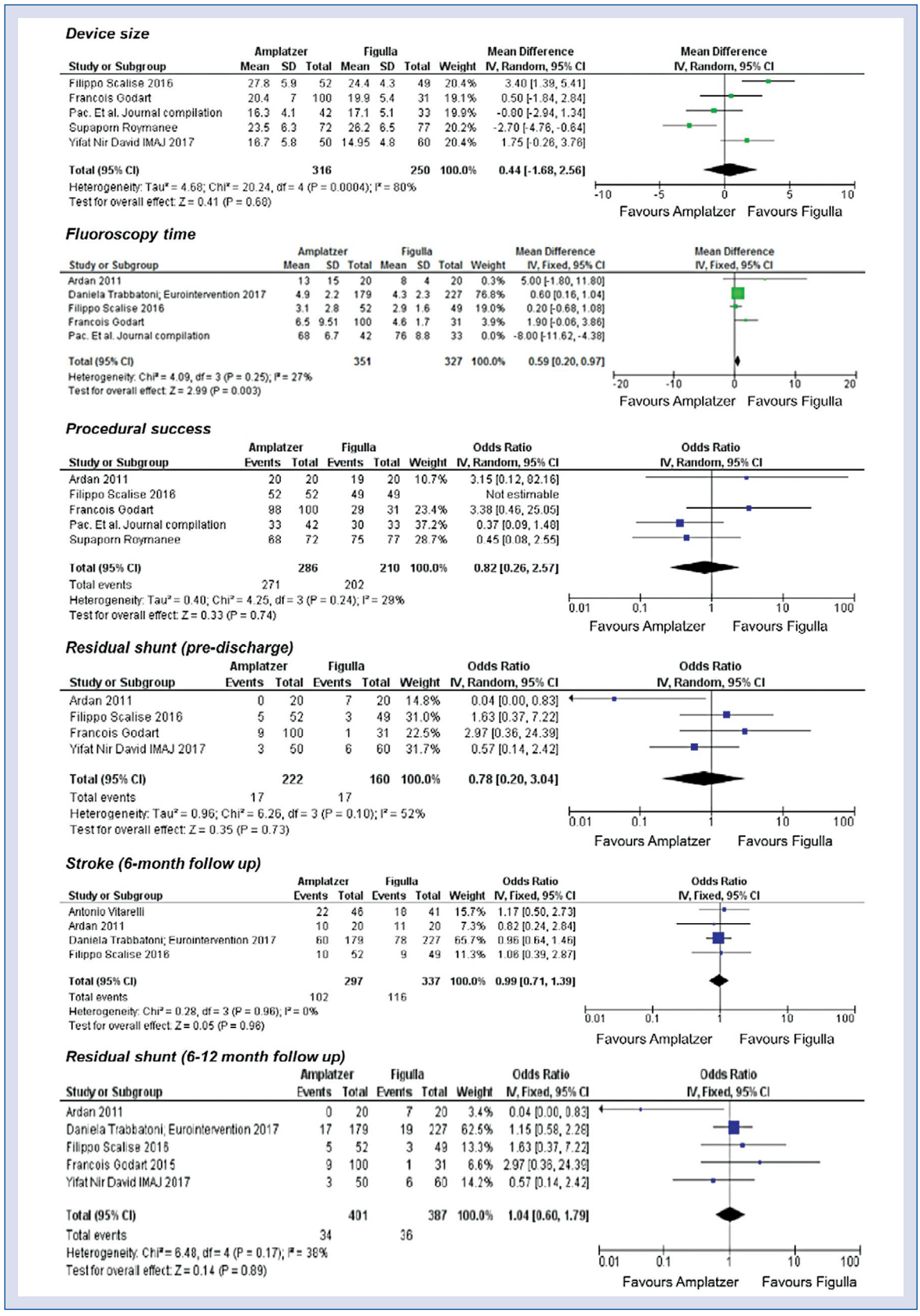

Figure 3. Forest plot reflecting procedural and follow-up outcomes of the patients included in the meta-analysis. *Vertical line represents "no difference" point between the Amplatzer and Figulla groups; Horizontal lines 95% confidence interval (CI). Squares represent odds ratio for each study (the size of each square denotes the proportion of information given by each study). Diamonds represent pooled odds ratios from all studies.

population, and they also presented with half the rate of supraventricular arrhythmias in follow-up, which might be explained by the properties of the FSO device with a less heavy mesh, likely diminishing the interaction with atrial tissue.

Baseline risk and post-procedural main complications

There was a higher prevalence of septal aneurysm among patients that underwent closure with ASO devices (32% vs. 25%, p = 0.061) which might partially explain the greater residual shunt detected with ASO in the peri-procedural transesophageal echocardiography. Pre-procedural screening and diagnosis of septal anomalies with transesophageal echocardiography has demonstrated an excellent specificity to diagnose and measure interatrial shunts [21–23] but also might be useful in determining which device is optimal for each patient. According to the present findings, those patients with baseline risk of residual shunt (i.e. larger defects, septal aneurysm) and those predisposed to supraventricular arrhythmias (i.e. larger atria or history of paroxysmal atrial fibrillation) might benefit more from a smoother device.

Percutaneous closure of the septal defects presented similar success rates to those reported in former studies (96–98%) [24]. The procedure is considered successful even in the presence of a mild residual shunt if the device is stable though it is well known that mild to moderate residual shunts might preclude from full endothelialization [5]. Indeed, current evaluation of residual shunting degree might present certain limitations when evaluating the impact on long-term outcomes. Although percutaneous closure presents a lower rate of complications as compared to surgical closure (7% vs. 24%), the presence of residual shunt and its associated risks (right heart overload, paradoxical emboli, supraventricular arrhythmia, etc.) might require surgical closure more often than thought. On the other hand, the absence of cases presenting cardiac erosion in this research is a reassuring finding but since that might appear even years after the procedure [24, 25] and is a life-threatening complication, any measure aimed to diminish that risk, as is the use of more flexible devices, ought to be considered [26].

Finally, the development of supraventricular arrhythmia is a classical concern in patients suffering from left-to-right blood shunting but, paradoxically, sometimes they can be triggered by the percutaneous closure device itself, likely due to local inflammation and scarring. In this regard, the potential variable impact of devices manufactured with different raw materials might explain the lower rate of this complication with the FSO [27, 28]. It is noted, this difference in the rate of supraventricular arrhythmias were not statistically significant when analyzed separately for PFO and congenital ASD but the persistence of a statistical trend also supports that this hypothesis which merits further investigation.

Uncommon complications: endocarditis, devices thrombosis and neurovascular events

Device implantation is performed under strict asepsia and with prior antibiotic prophylaxis [29] to lower the risk of device related infective endocarditis. However, this complication is occasionally reported in the literature [30]. Consensus has not been reached regarding adequate antibiotic prophylactic treatment but some authors suggest up to 6 months until endothelialization is completed (according to findings from animal models) [26], but also, the raw materials and structure of the devices might play a role. Similarly, device thrombosis is rare but could be additionally associated to the use of one material or another and its structure. However, more data are needed to verify this hypothesis since no differences were found in this research. Finally, neurovascular events have been related to the presence of residual shunts [27, 28] which was not uncommon in this analysis and should raise attention to the most adequate imaging tool to be used in follow-up and also stresses the importance of adequate sizing during the procedure; the use of ASO or FSO neither played a role on this complication and both were equally safe in this regard.

Limitations of the study

There are a number of limitations related to this work. First, the paucity of multicentric randomized studies and the typology of the compiled studies may somehow limit the external validity of the reported findings. Secondly, outcomes were reported only for up to 1 year but longer follow-up would be required to assess safety issues of concern. Finally, some of the gathered studies presented a lack of clear definition of major and minor complications and their underreporting could not be ruled out. Also, some of the studies had small sample sizes which may have had an impact on the results due to low operator experience with percutaneous closure of interatrial septal defects.

Conclusions

In this meta-analysis that included 11 non-randomized studies and > 1,800 patients undergoing ASD closure with both, the ASO or the FSO closure devices, safety and effectiveness were similar as well as global success rate. However, procedures were shorter with the FSO device and the rate of supraventricular arrhythmias in follow-up was lower. Importantly, no cases of late cardiac erosion were detected. Newer bioresorbable devices will need to demonstrate competitive results to those herein reported.

Conflict of interest: None declared

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Secondary prevention of coronary artery disease in Poland. Results from the POLASPIRE survey

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Abstract

Background: *The highest priority in preventive cardiology is given to patients with established coronary artery disease (CAD). The aim of the study was to assess the current implementation of the guidelines for secondary prevention in everyday clinical practice by evaluating control of the main risk factors and the cardioprotective medication prescription rates in patients following hospitalization for CAD.*

Methods: *Fourteen departments of cardiology participated in the study. Patients (aged ≤ 80 years) hospitalized due an acute coronary syndrome or for a myocardial revascularization procedure were recruited and interviewed 6–18 months after the hospitalization.*

Results: *Overall, 947 patients were examined 6–18 months after hospitalization. The proportion of patients with high blood pressure (≥ 140/90 mmHg) was 42%, with high low-density lipoprotein cholesterol (LDL-C ≥ 1.8 mmol/L) 62%, and with high fasting glucose (≥ 7.0 mmol/L) 22%, 17% of participants were smokers and 42% were obese. The proportion of patients taking an antiplatelet agent 6–18 months after hospitalization was 93%, beta-blocker 89%, angiotensin converting enzyme inhibitor or sartan 86%, and a lipid-lowering drug 90%. Only 2.3% patients had controlled all the five main risk factors well (non-smoking, blood pressure < 140/90 mmHg, LDL-C < 1.8 mmol/L and glucose < 7.0 mmol/L, body mass index < 25 kg/m^2), while 17.9% had 1 out of 5, 40.9% had 2 out of 5, and 29% had 3 out of 5 risk factors uncontrolled.*

Conclusions: *The documented multicenter survey provides evidence that there is considerable potential for further reductions of cardiovascular risk in CAD patients in Poland. A revision of the state funded cardiac prevention programs seems rational.* (Cardiol J 2020; 27, 5: 533–540)

Key words: coronary artery disease, risk factors, secondary prevention, smoking, hypertension, hypercholesterolemia

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Introduction

Coronary artery disease (CAD) is the single most common cause of death [1]. In recent years, a rapid development has been observed in pharmacological and invasive CAD treatment methods. Nevertheless, among acute myocardial infarction (MI) survivors, the one-year mortality rate following discharge from hospital in Poland is about 10% [2]. Several causes of this high mortality rate have been indicated, including inadequate lifestyle changes and poor control of risk factors, as well as inadequate pharmacotherapy [3]. Indeed, several surveys showed a considerable potential for further improvement in the field of secondary prevention in European countries, including Poland [4–7]. Interestingly, available data suggest beneficial trends in the control of some risk factors, while an adverse trend in others [8]. The guidelines regarding the management of risk factors have recently been updated [9–12], but little is known about what their impact was of on clinical practice in Poland.

The aim of the present study was to assess the implementation of recently published guidelines for secondary prevention in everyday clinical practice by assessing control of the main risk factors and the cardioprotective medication prescription rates in patients after hospitalization for CAD.

Methods

This study was carried out in four regions: one in the northern part of Poland, one in the central region and two in the south of the country. In each region, at least one teaching hospital and one municipal hospital took part in the survey. In total, 14 departments of cardiology from 12 different hospitals participated in the study. Seven departments were located in teaching and 7 in municipal hospitals. In each department medical records of consecutive patients hospitalized due to acute MI (with and without ST elevation), unstable angina, percutaneous coronary intervention (PCI) or scheduled for coronary artery bypass grafting (CABG) were reviewed and patients aged ≤ 80 years were identified retrospectively, excluding those who died during their in-hospital stay. If a patient was hospitalized more than once within the study period, only the first hospitalization was accepted as an index event. Centrally trained research staff undertook data collection using standardized methods and the same instruments in all centers. They reviewed patient medical notes, interviewed and examined the patients.

Participants were invited to take part in follow-up examinations 6 to 18 months after being discharged. Data on demographic characteristics, personal history of CAD, smoking status, blood pressure, fasting glucose, plasma lipids, and prescribed medications were obtained using a standardized data collection form. Smoking status was verified by the concentration of breath carbon monoxide using a smoker analyzer (Bedfont Scientific, Model Micro+). Persistent smoking was defined as smoking at the time of the interview among those who smoked during the month prior to the index event.

Patient height and weight were measured in a standing position without shoes or heavy outer garments, using standard scales with a vertical ruler (SECA). Body mass index (BMI) was calculated according to the following formula: BMI = weight [kg]/(height [m])^2. Waist circumference was measured using a metal tape horizontally in the mid-axillary line, midway between the lowest rim of the rib cage and the tip of the hip bone with the patient standing. Blood pressure was measured twice, on the right arm in a sitting position after at least 5 min of rest. For plasma lipid and glucose measurements a fasting venous blood sample was taken in the morning. For the present report, results of the analyses were done no later than 4 h after blood collection. was

The secondary prevention coefficient was calculated in the following way: for each controlled risk factor (non-smoking, blood pressure < 140/90 mmHg, low density lipoprotein cholesterol [LDL-C] < 1.8 mmol/L, glucose < 7.0 mmol/L, BMI < 25 kg/m^2) during follow-up examination one point was given. Additionally, one point was given for taking an antiplatelet agent and an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin II receptor antagonist. Thus, the secondary prevention coefficient could vary from 0 to 7. The survey protocol was approved by the institutional Bioethics Committees.

Data management

All data were collected electronically through web-based data entry using a unique identification number for the center and individual. Data were submitted via the Internet to the data management center where checks for completeness, internal consistency and accuracy were run.

Statistical analysis

Categorical variables were reported as percentages and continuous variables as means ±

Table 1. Characteristics of the study population.

	STEMI N = 166	NSTEMI N = 259	UA N = 256	PCI N = 413	CABG N = 54	P	Total N = 1148
Age, years ± SD	61.0 ± 10.3	65.6 ± 8.2	66.4 ± 8.1	65.8 ± 7.7	65.7 ± 6.9	< 0.001	64.9 ± 8.4
Sex:							
Men	74.7%	68.3%	65.2%	72.6%	85.25	< 0.05	70.9%
Women	25.3%	31.7%	34.8%	27.4%	14.8%		29.1%
Duration of education*, years ± SD	12.5 ± 3.1	12.2 ± 3.1	12.1 ± 3.0	12.8 ± 3.2	11.7 ± 3.3	< 0.05	12.4 ± 3.1
Employed*	41.9%	24.2%	28.65	31.0%	32.6%	< 0.05	30.7%
Index hospitalization in teaching hospital	83.2%	82.3%	67.3%	93.8%	100.0%	< 0.001	84.1%
Participation in a rehabilitation program following the index hospitalization	51.5%	36.9%	13.4%	16.2%	48.8%	< 0.001	26.4%
Specialization of the physician*:							
Cardiologist	86.6%	84.1%	79.3%	87.1%	90.1%	0.08	84.8%
General	80.6%	85.6%	88.5%	85.7%	90.7%	0.28	85.8%
Practitioner							
Diabetologist	9.7%	9.7%	12.0%	10.9%	9.3%	0.94	10.6%
Other physician	1.5%	2.1%	4.6%	3.1%	2.3%	0.45	3.0%
No regular check-ups	1.5%	0.5%	2.3%	0.05	0.0%	< 0.05	0.8%

*Among subjects who participated in the follow-up examination, as declared by the patients; CABG — coronary artery bypass grafting; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; SD — standard deviation; STEMI — ST-segment elevation myocardial infarction; UA — unstable angina

standard deviation. The Pearson χ^2 test was applied to all categorical variables. Normally distributed continuous variables were compared by using the Student t test or analysis of variance. Variables without normal distributions were evaluated using the Mann–Whitney U test or the Kruskal–Wallis analysis of variance. A two-tailed p value of less than 0.05 was regarded as indicating statistical significance.

Results

The medical records of 1148 patients were reviewed and included in the analyses, among them 840 (73.2%) were hospitalized in teaching and 308 (26.8%) in municipal hospitals. Characteristics of the study population are presented in Table 1. Patients from the ST-segment elevation MI (STEMI) group were the youngest, and the proportion of women was highest in the unstable angina group.

Cardioprotective drug prescription rates at discharge are shown in Table 2. The prescription rate of antiplatelet drugs, ACEI or angiotensin II receptor antagonists, calcium antagonists, diuretics, lipid-lowering drugs, and antidiabetic drugs differed between the index diagnoses and the prescription rate of anticoagulants was similar across all groups. Among patients hospitalized due to acute coronary syndrome 80.0% were prescribed two antiplatelet drugs at discharge, the highest proportion were among patients with STEMI and the lowest proportion among patients with the unstable group ($p < 0.001$). Acenocumarol or warfarin were prescribed to 5.1% of discharged patients, while heparin (including low-molecular-weight heparins) was prescribed to 3.8% of patients. New oral anticoagulants were prescribed to 7.8% of discharged patients. Overall, 98.9% of patients were prescribed at least one antiplatelet drug or anticoagulant, with a variation across groups of borderline significance (98.8% in STEMI, 97.3% in non-ST-segment elevation MI [NSTEMI], 97.3% in the unstable angina group, 99.8% in PCI, and 100% in CABG group, $p = 0.05$). ACEIs were prescribed to 78.0% of discharged patients and angiotensin II receptor antagonists to 10.8% of patients. Insulin was prescribed to 10.0% of discharged patients, whereas oral antidiabetic drugs were prescribed to 25.3% of patients, including metformin, which was prescribed to 23.2% of patients.

Out of the 1148 invited patients, 947 participated in the follow-up examination 6–18 months after

Table 2. Prescription rates of cardioprotective drugs at discharge.

	STEMI	NSTEMI	UA	PCI	CABG	P	Total
Antiplatelets:							
At least one agent	98.8%	96.1%	96.5%	99.8%	98.2%	< 0.01	98.0%
Two agents	94.6%	81.5%	63.7%	95.2%	27.8%	< 0.001	81.8%
Beta-blockers	92.8%	87.3%	91.4%	92.7%	96.3%	0.07	91.4%
ACEI/sartans	84.3%	86.5%	86.3%	94.0%	83.3%	< 0.001	88.7%
Calcium antagonists	7.8%	22.4%	28.9%	35.1%	35.2%	< 0.001	26.9%
Diuretics*	21.1%	41.7%	50.8%	47.9%	57.4%	< 0.001	43.7%
Potassium sparing diuretics	25.9%	20.9%	18.8%	20.6%	14.8%	0.35	20.7%
Lipid lowering drugs:	92.8%	91.9%	92.2%	97.6%	98.2%	< 0.01	94.4%
Statins	92.8%	91.1%	91.8%	97.3%	98.2%	< 0.01	94.1%
Fibrates	0.6%	1.5%	5.5%	5.1%	0.0%	< 0.01	3.5%
Ezetimibe	0.6%	1.2%	2.3%	1.2%	1.9%	0.60	1.4%
Antidiabetic agents	20.5%	30.5%	27.7%	38.3%	27.8%	< 0.001	31.1%
Anticoagulants	15.1%	17.0%	16.8%	16.0%	14.8%	0.98	16.2%

*Thiazides or loop diuretics; ACEI — angiotensin converting enzyme inhibitors; CABG — coronary artery bypass grafting; NSTEMI — non-ST--segment elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction; UA — unstable angina

Table 3. Proportions of patients who did not reach treatment goals 6–18 months after discharge.

	STEMI	NSTEMI	UA	PCI	CABG	P	Total
Smoking	21.9%	18.7%	10.6%	18.2%	14.0%	< 0.05	16.9%
Blood pressure ≥ 140/90 mmHg	41.9%	46.5%	42.4%	40.7%	23.3%	0.09	41.7%
LDL-C ≥ 1.8 mmol/L	57.5%	65.0%	66.4%	58.5%	69.8%	0.16	62.0%
Glucose ≥ 7.0 mmol/L	19.6%	24.9%	19.4%	21.7%	20.9%	0.70	21.5%
Body mass index ≥ 25 kg/m^2	87.3%	85.8%	87.0%	84.0%	76.9%	0.57	85.1%
Body mass index ≥ 30 kg/m^2	36.6%	47.2%	39.8%	44.1%	26.2%	0.06	41.9%
Waist ≥ 102 cm in men and ≥ 88 cm in women	57.5%	68.4%	69.6%	63.5%	48.8%	< 0.05	64.4%

CABG — coronary artery bypass grafting; LDL-C — low density lipoprotein cholesterol; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction; UA — unstable angina

being discharged from hospital. The mean period of time from discharge to the follow-up examination was 1.01 ± 0.30 years (in 52% of cases the period was greater than 1 year). Out of all participants, 16.1% declared that they were smokers. Additionally, 0.8% declared that they do not smoke, however, they had an increased concentration of breath carbon monoxide (> 10 ppm). Overall, 16.9% of the study participants were smokers. The smoking rate differed significantly across groups, the highest being in the ST-elevation group (Table 3). Among patients who smoked during the prior month before the index event, 55.8% were smoking 6–18 months after being discharged, with no significant difference between the groups (STEMI group: 46.7%, NSTEMI group: 56.3%, unstable angina group: 53.9%, PCI group: 61.5%, CABG group: 66.7%; p = NS). It was observed that 41.7% of participants had high blood pressure, 62.0% had high LDL-C level, 21.5% had fasting glucose ≥ 7.0 mmol/L, 41.9% were obese while 85.1% were overweight or obese 6–18 months after being discharged. Mean systolic blood pressure was 134.3 ± 20.3 mmHg, diastolic blood pressure was 79.9 ± 11.5 mmHg, mean LDL-C level was 2.18 ± ± 0.94 mmol/L, mean BMI was 29.5 ± 4.5 kg/m^2 and mean waist circumference 103.5 ± 11.7 cm in men and 100.0 ± 12.4 cm in women.

The majority of persistent smokers did not attempt to quit smoking following the index hospitalization (Table 4). Less than 1 in 7 participants was physically active at the recommended level,

Table 4. Patients' lifestyles at the time of interview 6–18 months after discharge (as declared by the patients).

	STEMI	NSTEMI	UA	PCI	CABG	P	Total
Persistent smokers having attempted to quit smoking since hospital discharge	6.7%	10.8%	4.3%	10.9%	0.0%	0.76	8.7%
Obese patients having attempted actively to lose weight in last month	49.0%	52.7%	58.1%	57.1%	45.4%	0.74	55.0%
Overweight or obese patients having attempted actively to lose weight in last month	41.9%	40.8%	40.1%	43.1%	32.3%	0.80	41.3%
Patients having regular physical activit 30 min on average five times a week	14.0%	15.2%	12.0%	14.2%	20.9%	0.62	14.2%
Patients trying to reduce salt intake	65.45	69.2%	66.8%	68.4%	72.1%	0.91	67.9%
Patients trying to reduce fat intake	73.5%	72.2%	70.1%	75.5%	72.1%	0.70	73.1%
Patients trying to reduce calories intake	57.4%	58.1%	58.5%	67.5%	67.4%	0.07	62.0%
Patients trying to increase vegetables and fruits intake	71.3%	71.2%	71.0%	72.7%	81.4%	0.71	72.2%

CABG — coronary artery bypass grafting; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction; UA — unstable angina

Table 5. Proportion of patients taking cardioprotective drugs 6–18 months after discharge from the hospital.

	STEMI	NSTEMI	UA	PCI	CABG	P	Total
Antiplatelets	94.2%	95.0%	88.0%	94.3%	93.0%	< 0.05	92.9%
Beta-blockers	88.3%	87.9%	86.6%	91.8%	95.4%	0.19	89.4%
ACEI/sartans	81.8%	86.4%	84.8%	90.3%	65.1%	< 0.001	85.9%
Calcium antagonists	15.3%	32.3%	29.5%	34.4%	20.9%	< 0.001	29.5%
Diuretics*	36.5%	53.5%	50.7%	40.8%	67.4%	< 0.01	49.0%
Potassium sparing diuretics	25.7%	28.8%	15.2%	15.3%	27.9%	< 0.001	20.2%
Lipid lowering drugs:	87.6%	90.4%	85.7%	94.0%	90.7%	< 0.05	90.3%
Statins	87.6%	89.4%	84.3%	94.0%	90.7%	< 0.01	89.8%
Fibrates	1.5%	1.5%	6.0%	4.6%	0.0%	< 0.05	3.6%
Ezetimibe	1.5%	2.0%	3.2%	2.8%	2.3%	0.84	2.5%
Antidiabetic agents	24.8%	35.9%	31.5%	38.6%	32.6%	0.05	34.1%
Anticoagulants	8.0%	15.2%	14.8%	15.6%	14.0%	0.23	14.15%

*Thiazides or loop diuretics; ACEI — angiotensin converting enzyme inhibitors; CABG — coronary artery bypass grafting; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction; UA — unstable angina

and about half of the obese patients had attempted to lose weight.

The proportion of patients taking antiplatelets, ACEIs/angiotensin II receptor antagonists, diuretics, lipid-lowering drugs, and antidiabetic agents at the time of the follow-up examination differed significantly between the indexed groups (Table 5). Acenocumarol or warfarin were prescribed to 5.4% of patients, low-molecular-weight heparins to 0.2% of patients, while 8.6% of patients were prescribed new oral anticoagulants. Overall, 97.0% of patients were prescribed at least one antiplatelet drug or anticoagulant, with a variation across groups of a borderline significance (94.9% in STEMI group, 98.0% in NSTEMI group, 94.9% in unstable angina group, 99.3% in PCI, and 100% in CABG group, $p = 0.05$). ACEIs were prescribed to 70.5% of patients and angiotensin II receptor antagonists to 15.4% of patients. Among all patients, 9.9% were prescribed insulin, whereas 30.4% were prescribed oral antidiabetic drugs, including metformin, which was prescribed to 28.3% of patients. A statin in combination with ezetimibe was prescribed to 2.3% whereas high dose statin in combination with

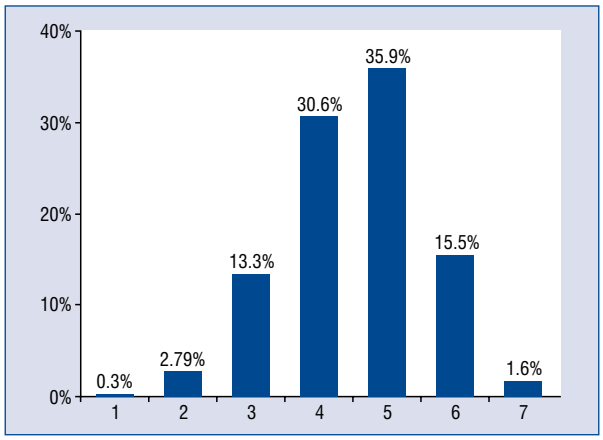

Figure 1. Distribution of the secondary prevention coefficient values.

ezetimibe to 1.8% of patients. A statin in combination with a fibrate was prescribed to 3.3% whereas high dose statin in combination with a fibrate to 1.8% of patients.

The mean secondary prevention coefficient was 4.52 ± 1.06 (median value: 5; interquartile range: 4, 5). Its value was equal to 7 in only 1.6% of patients, while 17.1% had a secondary prevention coefficient of at least 6 (Fig. 1). The secondary prevention coefficient value was related to age, employment and the specialization of the physician who, according to the patient, had decided about their management (Table 6). The secondary prevention coefficient was not related to sex, education, index diagnosis or hospitalization teaching hospitals. It was observed that only 2.3% of patients had all main risk factors well controlled (non-smoking, blood pressure < 140/90 mmHg, LDL-C < 1.8 mmol/L, glucose < 7.0 mmol/L, BMI < 25 kg/m^2), while 18.0% had 1 out of 5, 40.8% had 2 out of 5, and 29.0% had 3 out of 5 risk factors uncontrolled. Finally, 0.9% of study participants had all main risk factors uncontrolled.

Discussion

In general, results suggest a considerable potential for further reduction of cardiovascular risk in CAD patients. Recently, not much data concerning the quality of secondary prevention of CAD in Poland has been published. In a nation-wide registry of patients hospitalized due to MI, the prescription rate of statins, beta-blockers and ACEIs was comparable to results obtained in this study, whereas the prescription rate of antiplatelet drugs was slightly lower [13]. In a single center analysis

Table 6. The secondary prevention coefficient values according to subgroups of patients.

Subgroup	Secondary prevention coefficient ± SD	P
Age [years]:		< 0.01
< 60	4.36 ± 1.19	
60–70	4.50 ± 0.96	
≥ 70	4.65 ± 1.10	
Sex:		0.52
Men	4.54 ± 1.05	
Women	4.49 ± 1.09	
Duration of education [years]:		0.17
≤ 11	4.47 ± 1.05	
> 11	4.57 ± 1.07	
Index diagnosis:		0.19
STEMI	4.51 ± 1.11	
NSTEMI	4.41 ± 1.09	
Unstable angina	4.47 ± 1.01	
PCI	4.63 ± 1.06	
CABG	4.50 ± 1.04	
Index hospitalization in a teaching hospital:		0.46
Yes	4.53 ± 1.06	
No	4.46 ± 1.07	
Rehabilitation program following the index hospitalization:		0.12
Participated	4.61 ± 1.01	
Not participated	4.49 ± 1.08	
Specialization of the physician:		< 0.05
Cardiologist	4.57 ± 1.06	
Other physician	4.30 ± 1.05	
No regular health check-ups	4.13 ± 1.13	
Professionally active	4.49 ± 1.07	< 0.05
Professionally inactive	4.66 ± 1.03	
Total	4.52 ± 1.06	

STEMI — ST-segment elevation myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; CABG — coronary artery bypass grafting; SD — standard deviation

of patients undergoing CABG, the use of antiplatelets, ACEIs or angiotensin II receptor antagonists and statins were slightly lower when compared to prescription rates in the CABG group in the

present study [14]. Furthermore, two surveys, which included patients hospitalized due to CAD in 2011–2013 showed very similar prescription rates at discharge, and significantly lower cardioprotective drug usage in the post discharge period compared to the present study [15, 16]. The control of main cardiovascular risk factors was at similar levels [14, 15]. Results of the EUROASPIRE V survey were recently published [5]. Generally, the average control of main risk factors in 81 centers from 27 countries were worse compared to the results obtained in the present survey (e.g. smoking rate 19% vs. 17%, high LDL-C 71% vs. 62%), with the exception of blood pressure, which was controlled at a very similar level. Similar conclusions can be drawn from a comparison of Polish patients with stable CAD with patients from other European countries participating in the CLARIFY registry [17].

Although BMI, waist, and LDL-C level were the worst controlled risk factors (Table 3), it should be emphasized that the present results suggest insufficient control of all main cardiovascular risk factors. The present results confirm the previous suggestion that sex and index diagnosis are not related to the secondary prevention goal achievement in clinical practice, at least in Poland [15]. Interestingly, hospitalization in a teaching hospital was not significantly related to the secondary prevention coefficient. Results from the present study suggest that patients managed by cardiologists achieve the recommended secondary prevention goals more often. Although the influence of a number of confounders cannot be excluded, including income. The WOBASZ study also showed specialists more often provide preventive support as compared to general practitioners [18]. Although based on the present results, a cause-and-effect relationship cannot be proved, it was suggested that cardiologist care is associated with lower mortality following acute coronary syndrome [19].

Organizational interventions for the secondary prevention of CAD have been shown to reduce mortality in CAD patients, further, experts of the Polish Cardiac Society have recently announced a new organizational system named "Managed care after myocardial infarction" [3, 20]. The system consists of four modules: complete revascularization, education and rehabilitation program, electrotherapy including implantable cardioverter-defibrillators, biventricular pacing when appropriate and periodical cardiac consultations, which last 12 months. It also contains a quality of care assessment based on clinical measures (e.g. risk factor control, rate of complete myocardial revascularization, etc.), as well as rate of cardiovascular events [3]. Preliminary results of the new system are encouraging [21].

Limitations of the study

The present study had some limitations. Firstly, was the inability to assess the impact of implementing secondary prevention guidelines on the risk of cardiovascular complications. Secondly, participants of the present study were not representative of all CAD patients. Participants were limited to those who had experienced an acute CAD event or had undergone a revascularization procedure. Therefore, the present results should not be directly applied to other CAD patients. Thirdly, only patients aged ≤ 80 years were studied, therefore results should not be applied directly to older patients. Fourthly, assessment of risk factor control at the discharge from hospital could not be done. Finally, the doses of cardioprotective drugs taken by patients were not analyzed. It is possible that blood pressure, lipids, and glucose were not controlled in some cases due to insufficient doses of the prescribed drugs. It should also be noted that no information on the patient compliance with instructions regarding prescriptions was lacking. It is reasonable to suspect that some patients had been taking their medications irregularly [22–24]. According to a previously published study patients' self-reported drug intake is often misleading, as in over 40% of subjects reporting regular intake of prescribed drugs objective assessment did not confirm this statement [25]. However, an important advantage of the analysis is that results are not based just on abstracted medical record data but on face-to-face interviews and examinations using the same protocol and standardized methods and instruments. Therefore, this analysis provides reliable information on lifestyle, risk factors, and therapeutic management for secondary prevention of CAD.

Conclusions

This multicentre survey provides evidence that there is a considerable potential for further reduction of cardiovascular risk in CAD patients in Poland. A revision of the state funded cardiac prevention program seems rational.

Conflict of interest: None declared

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Impact of air pollution on hospital patients admitted with ST- and non-ST-segment elevation myocardial infarction in heavily polluted cities within the European Union

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Abstract

Background: *Air pollution triggered diseases have become a leading health problem worldwide. The main adverse effects of air pollutants on human health are related to the cardiovascular system and particularly show an increasing prevalence of myocardial infarct and stroke. The aim of the study was to evaluate the influence of main air pollutants on non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI) admissions to local interventional cardiology centers.*

Methods: *Between 2014 and 2015, a multicenter registry of 1957 patients with acute myocardial infarction (STEMI, NSTEMI) admitted to interventional cardiology departments in three Polish cities were under investigation. The air pollution (PM2.5, PM10, NO2, SO2, O3) and weather conditions (temperature, barometric pressure, humidity) data for each city were collected as daily averages. The case-crossover design and conditional logistic regression were used to explore the association between acute myocardial infarctions and short-term air pollution exposure.*

Results: *Occurrence of NSTEMI on the day of air pollution was triggered by PM2.5 (OR = 1.099, p = 0.01) and PM10 (OR = 1.078, p = 0.03). On the following day after the air pollution was recorded, NSTEMI was induced by: PM2.5 (OR = 1.093, p = 0.025), PM10 (OR = 1.077, p = 0.025) and SO2 (OR = 1.522, p = 0.009). For STEMI, events that occurred on the day in which air pollution was triggered by: PM2.5 (OR = 1.197, p < 0.001), PM10 (OR = 1.163, p < 0.001), SO2 (OR = 1.670, p = 0.001) and NO2 (OR = 1.287, p = 0.011). On the following day after air pollution was recorded, STEMI was induced by: PM2.5 (OR = 1.172, p < 0.001), PM10 (OR = 1.131, p = 0.001), SO2 (OR = 1.550, p = 0.005) and NO2 (OR = 1.265, p = 0.02). None of the weather conditions indicated were statistically significant for acute myocardial infarction occurrence.*

Conclusions: *The most important pollutants triggering acute myocardial infarction occurrence in the population of southern Poland, both on the day of air pollution and the following day are particulate matters (PM2.5, PM10) and gaseous pollutants including NO2 and SO2. These pollutants should be regarded as modifiable risk factors and thus, their reduction is a priority in order to decrease total morbidity and mortality in Poland.* (Cardiol J 2020; 27, 5: 541–547)

Key words: air pollution, myocardial infarction, non-ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI)

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Introduction

Air pollution triggered diseases have become a leading problem both in well-developed and for emerging economy countries. According to The World Health Organization 3.7 million deaths per year occur from exposure to outdoor air pollution [1]. What is more, 72% of air pollution-related premature deaths were due to ischemic heart disease and strokes [2]. This confirms, that the cardiovascular system is one of the most susceptible human body systems affected by ambient air pollution.

Outdoor air pollution is particularly driven by industry, transport (especially diesel engines) and other combustion processes such as heating and power generation devices. It consists of particulate matter (PMs) and gaseous pollutants — carbon monoxide (CO), sulfur dioxide (SO2), nitrogen dioxide (NO2) and ozone (O3). PMs can be further divided according to their diameter to PM10 ($\leq 10\ \mu$m), PM2.5 ($\leq 2.5\ \mu$m).

Previous studies have explored the association between acute myocardial infarctions (AMIs) and air pollution. The results were conflicting. Some of them have shown an association between AMIs and some air pollutants, especially PM2.5, PM10, SO2 and NO2 [3]. The main pathology mechanism of air pollution affecting the cardiovascular system includes systemic and local oxidative stress and inflammation that triggers endothelial dysfunction, platelet hyperreactivity and impaired vascular fibrinolytic function [4]. The local mechanism is caused by gases and soluble components of particulate matter, especially those with the smallest diameter which can easily cross the pulmonary epithelium and get into the blood stream. The systemic pathway is activated by pulmonary inflammation and oxidative stress, which was confirmed by the increasing level of pro inflammatory cytokines in the animal and human studies after short exposure to air pollutants [5]. Moreover, in experimental studies the autonomic imbalance favoring sympathetic activation leads to arrhythmia, vasoconstriction and hypertension [6].

All of these mechanisms may accelerate atherosclerosis, plaque instability and promote atherothrombosis, resulting in AMI and sudden death in short, as well as long-term observation. From an epidemiological point of view, the air pollutants are of important meaning as they can be qualified as modifiable risk factors of myocardial infarct and the prevention of air pollution should be included in national programs of cardiovascular disease prevention.

On the other hand, some non-modifiable factors have been considered to be triggering AMIs such as weather conditions [7]. Among meteorological variables, temperature [8] and barometric pressure [9] have been found to be prominently associated with myocardial infarction.

Thus, it is of great importance to further investigate the influence of major air pollutants and meteorological variables which effect health status. The evaluation may be especially valuable when performed in the most polluted areas where the scale of affect seems to have the strongest effect and may be more easily measured. It is also important to measure the effect in large enough and similar populations, based on serial observations that take into account not only polluted days but also refer to the periods of normal weather conditions.

Despite having a well-developed structure for optimal AMI treatment, Poland has been qualified as one of the European Union countries with highest rate of MI, stroke event rate and cardiovascular mortality. At the same time, Poland is one of the most air polluted countries in Europe, where fossil fuel is a major source of energy and the role of air pollution is underestimated [10]. This situation has prompted this study to perform an analysis that can evaluate the influences of all commonly measured air pollutants and weather condition parameters, separately on non-ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI) occurrence based on data selected from three typical, Polish, small and medium sized industrial cities.

Methods

Database

This study draws from a multicentre registry of AMI of three American Heart of Poland centers located in industrial cities in southern Poland: Kedzierzyn-Kozle (fifty-eight thousand inhabitants), Bielsko-Biala (one hundred seventy thousand inhabitants) and Mielec (sixty-two thousand inhabitants). Based on recently published registries these regions have qualified as some of the most air polluted regions in Europe [11]. Data collection covered a period from January 2014 to December 2015 from the regions of Bielsko-Biala, July 2014 to December 2015 from Kedzierzyn-Kozle and January 2015 to December 2015 from Mielec. The differences in these analyzed periods between centers are the result of different onset of air-quality monitoring in each city. All reported

Table 1. Air quality in selected cities [11].

Center	Days above PM2.5 (25 μm/m^3) limit (% of tested period)	Annual mean of PM2.5	Days above PM10 (50 μm/m^3) limit (% of tested period)	Annual mean of PM10	Place in WHO report
Bielsko-Biala	233 days (34%)	34 μm/m^3	142 days (21%)	41 μm/m^3	32
Kedzierzyn-Kozle	187 days (43%)	33 μm/m^3	80 days (18.5%)	39 μm/m^3	37
Mielec	132 days (38%)	31 μm/m^3	61 days (18%)	42 μm/m^3	56

WHO — World Health Organization

data come from local departments of interventional cardiology, which are the only centers providing 24/7 services in their regions. In the clinical data, both types of myocardial infarction admissions (STEMI and NSTEMI) were collected. The types of AMIs were established based on clinical data reported to the National Health Fund.

The air pollution and weather condition data for each city were collected as daily averages from a database audited by the Chief Inspectorate of Environmental Protection in Poland. The following parameters were assembled: PM2.5, PM10, NO2, SO2, O3, barometric pressure, temperature and humidity. The cities were selected for this study based on the most complete and accurate data from air pollution measuring stations.

In order to present daily trends in particulate matter, concentrations over the analyzed period of time and were combined with the trends in the incidence of MIs. The data was further divided into PM2.5 and PM10 consecutive thresholds in which each an increase in concentration of 10 μm/m^3 was translated into a higher threshold. In this division, the daily limit for PM2.5 (25 μm/m^3) was included in threshold 3 while the limit for PM10 (50 μm/m^3) was in threshold 6.

Statistical analysis

The case-crossover design was used to explore the association between each type of AMI and air pollution exposure. In this type of analysis each case provides its own control, eliminating the influence of time-independent covariates, for instance hypertension, smoking, hypercholesterolemia and others [12]. The value of each pollutant, barometric pressure, temperature and humidity during the day of MI occurrence or the previous day to MI were considered in each case. The median level of each of the above-mentioned variables from the 7 days prior to MI were taken as a control. The present study was focused on the short-term influence of each variable on NSTEMI or STEMI occurrence, and was restricted to the day of exposure (day 0) and the following day after exposure (day 1).

In statistical analysis, conditional logistic regression was used to assess the odds ratio (OR) with 95% confidence intervals (95% CI). Analysis was performed for a 10 μm/m^3 increase in air pollutants, 10°C increase in temperature, 10% increase in humidity and 10 mmHg change in the barometric pressure. The correlation between air pollutants and weather conditions were calculated using the Spearman correlation. P value ≤ 0.05 was considered as statistically significant.

Results

The air quality in all cities were comparable based on the latest World Health Organization (WHO) report [11] and measurements of air pollutants (Table 1). Full data on air pollution measurement were available for 89% (1462 days) over the observation time period and 1957 cases of MI were analyzed. Precise characteristics of data collected are seen in Table 2. The reason for days missing was the lack of respective measurements of air quality due to periodic failures of local pollution measuring stations. If any measurement was missing during this period, it was excluded from study.

NSTEMI was presented during 686 days with complete, available pollution measurements and its total was 985 cases. STEMI was presented during 666 days with complete, available pollution measurements and the total number of cases was 972. Daily means of incidences in all centers were as follows: NSTEMI 0.67 ± 0.86 cases, STEMI 0.66 ± 0.87 cases and AMI's 1.33 ± 1.24 cases. Detailed information about daily mean incidence occurrence was separate for all cities and are represented in Table 3.

The main descriptive statistics for variables are presented in Table 4. The correlations between variables are presented in Table 5. The highly positive correlations were observed between PM2.5

Table 2. Main characteristic of data collected from different centers.

Center	Period	Available data (%)	MI cases	NSTEMI cases	STEMI cases
All centers	1644 days	1462 days (89%)	1957	985	972
Bielsko-Biala	2014–2015 (730 days)	682 days (93%)	1185	561	624
Kedzierzyn-Kozle	July 2014–2015 (549 days)	433 days (79%)	443	252	191
Mielec	2015 (365 days)	347 days (95%)	329	172	157

MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction

Table 3. Mean daily occurrence of acute myocardial infarction.

Center	MI daily	NSTEMI daily	STEMI daily
All centers	1.33 ± 1.24	0.67 ± 0.86	0.66 ± 0.87
Bielsko-Biala	1.73 ± 1.35	0.82 ± 0.95	0.91 ± 0.99
Kedzierzyn-Kozle	1.02 ± 1.03	0.58 ± 0.77	0.44 ± 0.68
Mielec	0.95 ± 1.02	0.49 ± 0.74	0.45 ± 0.70

Data are shown as mean ± standard deviation. MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction

Table 4. Descriptive statistics for each variable measured.

Variable	Median	Minimum	Maximum	Mean	± SD
PM2.5 [$\mu m/m^3$]	20	3	256	27.59	22.89
PM10 [$\mu m/m^3$]	27	5	260	35.41	26.26
SO2 [$\mu m/m^3$]	5	0.7	80	7.56	6.63
NO2 [$\mu m/m^3$]	16	3	69	17.80	8.55
O3 [$\mu m/m^3$]	51	1	127	50.26	23.84
Barometric pressure [hPa]	987	932	1021	984.04	15.36
Temperature [°C]	9	–18	29	9.64	8.06
Humidity [%]	78	31	99	77.25	14.21

PM2.5 — particulate matter with diameter < 2.5 μm; PM10 — particulate matter with diameter < 10 μm; SO2 — sulfur dioxide; NO2 — nitrogen dioxide; O3 — ozone; SD — standard deviation

Table 5. Spearman correlations between variables. All statistically significant correlations are highlighted.

Variable	PM10	PM2.5	SO2	NO2	O3	Barometric pressure	Temperature	Humidity
PM10	1.00	0.90	0.64	0.71	–0.47	0.21	–0.40	0.09
PM2.5	0.90	1.00	0.61	0.65	–0.51	0.21	–0.43	0.16
SO2	0.64	0.61	1.00	0.59	–0.41	–0.10	–0.63	0.19
NO2	0.71	0.65	0.59	1.00	–0.60	–0.02	–0.38	0.32
O3	–0.47	–0.51	–0.41	–0.60	1.00	–0.18	0.56	–0.64
Barometric pressure	0.21	0.21	–0.10	–0.02	–0.18	1.00	0.12	–0.34
Temperature	–0.40	–0.43	–0.63	–0.38	0.56	0.12	1.00	–0.49
Humidity	0.09	0.16	0.19	0.32	–0.64	–0.34	–0.49	1.00

PM2.5 — particulate matter with diameter < 2.5 μm; PM10 — particulate matter with diameter < 10 μm; SO2 — sulfur dioxide; NO2 — nitrogen dioxide; O3 — ozone

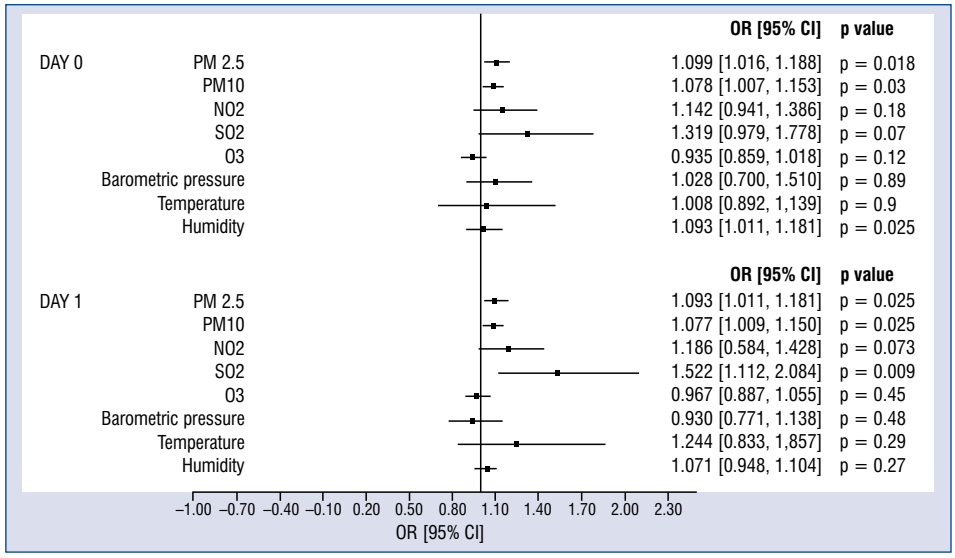

Figure 1. Logistic regression model for non-ST-segment elevation myocardial infarction (NSTEMI) occurrence; PM2.5 — particulate matter with diameter < 2.5 μm; PM10 — particulate matter with diameter < 10 μm; SO2 — sulfur dioxide; NO2 — nitrogen dioxide; O3 — ozone; OR — odds ratio; CI — confidence interval.

and PM10 (R = 0.9) or PM10 and NO2 (R = 0.71), respectively. The intermediate or negative correlations were for O3 and humidity (R = –0.64), SO2 and temperature (R = –0.63), O3 and nitrogen oxides (R = –0.63 for NO and –0.6 for NO2).

NSTEMI

In the main analysis, both particulate matters including PM2.5 and PM10 had significant influence on NSTEMI occurrence on the day of air pollution exposure (OR = 1.099, CI 1.016–1.188, p = 0.018 for PM2.5 and OR = 1.078, CI 1.007–1.153, p = 0.03 for PM10). Moreover, during the following day after air pollution, the exposure that triggered NSTEMI occurrence included SO2 (OR = 1.522, CI 1.112–2.084, p = 0.009) and both types of particulate matters: PM2.5 (OR = 1.093, CI 1.011–1.181, p = 0.025), PM10 (OR = 1.077, CI 1.009–1.150, p = 0.025). An extensive analysis for NSTEMI is presented in Figure 1.

STEMI

The most important triggers for STEMI occurrence on the day of air pollution were gaseous pollutants including SO2 (OR = 1.670, CI 1.230–2.266, p = 0.001), NO2 (OR = 1.287, CI 1.061–1.562, p = 0.011) and both particulate matters: PM2.5 (OR = 1.197, CI 1.094–1.311, p < 0.001) and PM10 (OR = 1.163, CI 1.079–1.253, p < 0.001). Similar results were seen on the following day after exposure and included SO2 (OR = 1.550, CI 1.140–2.108, p = 0.005), NO2 (OR = 1.265, CI 1.041–1.538, p = 0.018), PM2.5 (OR = 1.172, CI 1.076–1.276, p < 0.001) and PM10 (OR = 1.131, CI 1.053–1.215, p < 0.001). Detailed results for STEMI are presented in the Figure 2.

None of the weather conditions including temperature, barometric pressure and humidity reached statistical significance regarding to both types of MI and time periods.

Discussion

According to the latest WHO report, Poland is the most air-polluted region among European Union countries [11]. At the beginning of 2017, measured concentrations of PM2.5 and PM10 in some regions of Poland reached over 30 times recommended limits. The values had never been observed thus far in past years. Interestingly, this deterioration in air quality coincided with almost , fourteen thousand additional deaths in Poland compared to demographic data from January to February years 2016 and 2017 (Table 6, Based on Polish Central Statistical Office data) [13].

Confirmation of this serious situation in selected Polish cities are recorded in maximum values of air pollutants in Table 1, where the guideline limits are exceeded by up to 1000%. What is more, analyzing Table 3, during tested period about 35% of these days were above the daily limit of PM2.5. In addition, there is a lack of sufficient governmental action over the last decades to limit gas and dust

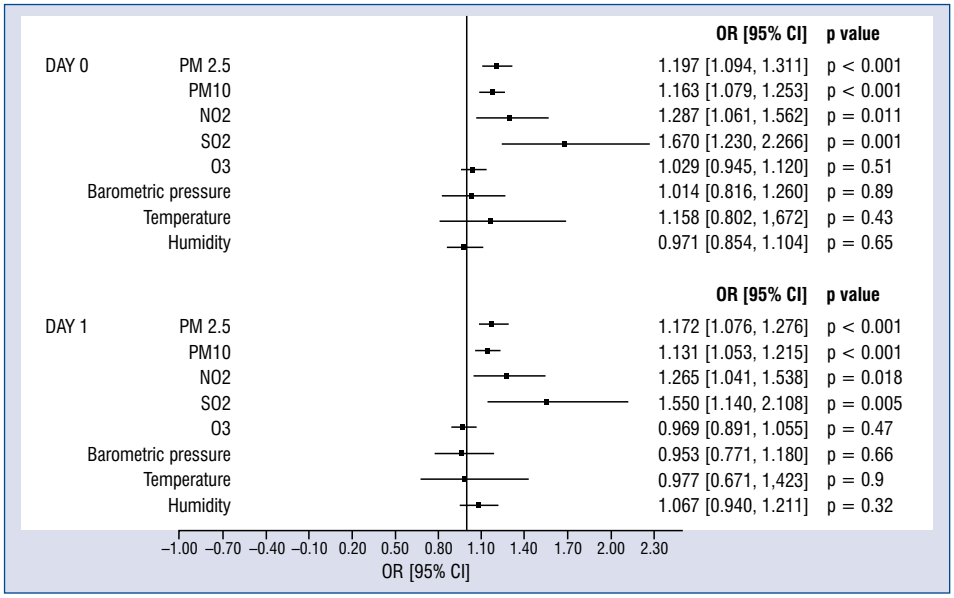

Figure 2. Logistic regression model for ST-segment elevation myocardial infarction (STEMI) occurrence; PM2.5 — particulate matter with diameter < 2.5 μm; PM10 — particulate matter with diameter < 10 μm; SO2 — sulfur dioxide; NO2 — nitrogen dioxide; O3 — ozone; OR — odds ratio; CI — confidence interval.

Table 6. Differences in Polish population statistics [13].

Month	2016	2017	Change in amount (%)
January	33,000	44,400	+11,400 (+35%)
February	34,900	37,400	+2,500 (+7%)
Total	67,900	81,800	+13,900 (+20.5%)

emissions, leading to systematic worsening of air pollution in Poland.

In the currently available literature, there remains a lack of studies examining the role of air pollution on MI occurrence in such polluted regions. In addition, only a few worldwide studies which have evaluated the influence of air pollution separately on NSTEMI and STEMI events. Most of the analyses were focused only on the impact of the particulate matters and overlooked the weather influence and gaseous pollutants. The present study takes into consideration a large number of air pollutants and weather conditions including: temperature, barometric pressure and humidity. It is also important to evaluate the influence of air pollution on AMI occurrence in the setting of a local environment. These features, as well as the number of variables and data taken into analysis from three different centers and cities make this study precise and plausible.

The present study found differences in the level of air pollution and its influence on each type of MI occurrence. These results have presented that the STEMI events are especially associated with particulate matters: PM10, PM2.5 and gaseous pollutants: SO2 and NO2. From particulate matters, the PM2.5 played the main role, which concurs with findings reported by other researchers [14]. Similar effects were seen during both examining days, which provides evidence that air pollution essentially has an impact on STEMI events. Comparable results of air pollution influence on STEMI occurrence were reported by other studies. Argacha et al. [15] found an association between STEMI and both particulate matters and NO2, which had the most significant impact, but SO2 was not included in this study. Pope et al. [16] in a large study, also found a similar association between STEMI and PM2.5 which was the only pollutant evaluated in the analysis.

On the other hand, weaker relationships were seen between air pollution and NSTEMI occurrence. Only particulate matter turn out to be statistically significant during the day of exposure to air pollution. The day after exposure, the importance in triggering NSTEMI had been reached by: PM10, PM2.5 and SO2. In the literature there are only a few studies showing evidence of air pollution influence on NSTEMI occurrence. This can be caused by the especially small number of studies

exploring both types of AMI separately. Only the association between NSTEMI and daily maximum 1-h level of NO2 was confirmed by Butland et al. [17], but in this study the SO2 was not evaluated. Present findings regarding NSTEMI may also be caused by the high level of air pollution in Poland, which can exert significant influence on its appearance.

What is more, current results observed higher values of odds ratios for each 10 um/m^3 increase in gaseous pollutants than PMs. This can be explained by a lower spread of its minimal and maximal levels, compared to other pollutants, mainly PM's. These findings confirm, that not only PMs play role in triggering MI, but the most dangerous for human health is a combination of gaseous pollutants, especially SO2 and NO2 with PMs, above PM2.5.

To summarize, the results of the current study clearly show that air pollution should be regarded as one of the modifiable risk factors of cardiovascular diseases that are the main cause of mortality in western countries and contribute to a serious economic burden with substantial loss of productivity and Gross Domestic Product value. Only coordinated governmental and local actions focused on air quality improvement in combination with an increase in health care expenditures may significantly improve the quality of life for patients, reduce total mortality rate, and positively influence the economy. Unfortunately, in many countries the problem remains underestimated causing a serious health threat. For instance, despite the fact that Poland is the most air-polluted region among European Union countries, the government instead of setting a priority for making air cleaner has recently and dangerously reduced expenditures on cardiology and the development of green energy production, putting patients at serious risk of increased mortality and morbidity.

Limitations of the study

The current study has some limitations. In a case-crossover design, the choice of a control period is crucial for results. A median value was taken of each variable for 7 days preceding MI occurrence. It seems to be the most neutral value, which can present the short-term changes in air quality and weather conditions. The study also has the same weakness, such as a lack of carbon monoxide levels, which theoretically can also impact MI occurrence.

Conclusions

The most important pollutants triggering STEMI and NSTEMI occurrence in three populations of southern Poland, both on the day of air pollution and the following day are particular PM2.5 and PM10 matter and gaseous pollutants including NO2 and SO2. These pollutants should be regarded as modifiable risk factors and thus their reduction is a priority in order to decrease total morbidity and mortality.

Conflict of interest: None declared

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ORIGINAL ARTICLE

Low molecular weight heparin in surgical valve procedures: When and how much for an optimal prophylaxis?

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Abstract

Background: *Periprocedural antithrombotic prophylaxis in patients undergoing surgical valve procedures (SVP) is insufficiently investigated. Low molecular weight heparin (LMWH) has been considered as an alternative to unfractionated heparin (UFH). However, safety and efficacy of this prophylaxis strategy is unknown. This study aimed to investigate safety and efficacy of periprocedural LMWH prophylaxis and determine optimal dosage and timing for periprocedural cessation and initiation.*

Methods: *The present study is a retrospective, single-center observational analysis of 388 patients who underwent SVP (valve replacement or valvuloplasty) between 2015 and 2016. In-hospital endpoints were bleeding, transfusions, reoperation due to bleeding, and thromboembolic events.*

Results: *Giving the first dose of LMWH on the day of SVP was a risk factor for bleeding (OR 1.07; 95% CI 1.04–1.10; $p < 0.001$), transfusions (OR 1.04; 95% CI 1.01–1.07; $p = 0.008$) and reoperation due to bleeding (OR 1.20; 95% CI 1.12–1.28; $p < 0.001$), with > 40 mg/day as a predictor. A higher dosage of LMWH premedication was an independent risk factor for bleeding (OR 1.02; 95% CI 1.00–1.04; $p = 0.03$) and transfusion (OR 1.03; 95% CI 1.01–1.05; $p = 0.01$), with > 60 mg/day as a predictor for these events. LMWH dosed within 24 h prior to SVP increased the risk of transfusion (AUC 0.636; 95% CI 0.496–0.762; $p = 0.04$).*

Conclusions: *Bleeding is an important early concern after surgical valve procedures. Safety and efficacy of periprocedural prophylaxis with LMWH depends on dosage and the timing of its administration. The most optimal periprocedural prophylaxis in the SVP population appears to be LMWH in dosage of 40–60 mg/day, which is recommended for deep vein thrombosis prophylaxis, ceased at least one day before SVP.* (Cardiol J 2020; 27, 5: 548–557)

Key words: surgical valve procedure, bleeding complications, antithrombotic prophylaxis

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Introduction

Thromboembolic and bleeding events account for nearly three-quarters of early complications after surgical valve replacement (SVR) [1]. The risk of thromboembolic events is the highest in the first days after the procedure, reaching 4–8 cases per 100 patient-years [1–8]. However, the most common and life-threatening complication within the first 72 h after SVR is bleeding [1, 2, 9–12], which results from procedure-related coagulopathy caused by excessive consumption of plasma coagulation factors, enhanced platelet and fibrinolytic pathways activation during cardiopulmonary bypass (CPB), as well as a prolongation of coagulation cascade related to hypothermia [1, 13]. The risk of bleeding is further increased by the need for anticoagulation with unfractionated heparin (UFH) during SVR, reversal of its action with protamine sulfate, and its recirculation within 24 h after SVR [14, 15]. Although the early postprocedural period is burdened with a high risk of bleeding, antithrombotic prophylaxis is nevertheless required at the onset of SVR to avoid prosthesis thrombosis. There is a paucity of evidence guiding optimal antithrombotic prophylaxis after SVR and current recommendations are inconsistent in this regard [8, 15–19]. The European Society of Cardiology (ESC) recommends UFH as the first line prophylaxis early after SVR, while subcutaneous low molecular weight heparin (LMWH) is considered as off-label [16]. There is a growing body of evidence from observational studies that suggests that prophylaxis with LMWH after SVR is as safe and as effective as UFH while also having an advantage of easier administration [1, 9–11]. The optimal dosage and timing of LMWH initiation after SVR remains unknown. There are scant evidence-based recommendations available for periprocedural antithrombotic prophylaxis in surgical valvuloplasty [16]. Adequate periprocedural antithrombotic prophylaxis in patients undergoing SVR is an unmet clinical need that requires further investigation.

Therefore, this study aims to evaluate the safety and efficacy of periprocedural LMWH and to determine optimal dosage and timing of LMWH cessation before and initiation after surgical valve procedures (SVP).

Methods

This was a single-center, retrospective observational analysis. All consecutive patients who underwent elective SVP including SVR, valvuloplasty, combined valve procedure with coronary artery bypass grafting (SVP+CABG), or with concomitant ascending aorta replacement between January 2015 and January 2016 were included. Patients who required aortic valve replacement due to aortic dissection, periprocedural intra-aortic balloon counter pulsation or hemodialysis due to severe perioperative renal insufficiency were excluded. Prosthesis selection (biological vs. mechanical) was based on currently recommended consensus guidelines, including previous indications for chronic anticoagulation [16]. Surgical procedures were performed with UFH to maintain an activated clotting time (ACT) above 400 s during CPB. After the procedure, protamine sulfate was given for reversal of UFH in a 0.8–1:1 ratio. In the event of an ACT > 130 s during postoperative recovery, additional doses of protamine or tranexamic acid were administered at the surgeon's discretion. Two or three surgical drains (36 French) were placed around the heart and in the pleural cavities. Unless the drainage was not increased, drains were removed 1 day after SVP. Patients stayed in the intensive care unit or step-down unit until the second postoperative day. The two epicardial electrodes placed during SVR were removed on the third postoperative day.

The present institutional protocol herein, for periprocedural antithrombotic prophylaxis, consisting of LMWH therapy without anti-Xa factor monitoring, was utilized for all patients included in the present analysis. The timing of cessation, timing of initiation, and dosage of LMWH before and after SVP were based on current guidelines and individualized based on the surgeon's discretion, type of procedure, degree of achieved hemostasis, patient clinical condition, thromboembolic risk, body weight, and renal function [8, 15–19]. In the current protocol, LMWH was started 8–12 h after SVP with prophylactic dosages of 40–60 mg on the day of SVP and 40–80 mg on the first postoperative day, and then therapeutic dosages at 12-h intervals from the second postoperative day onwards. Oral anticoagulation (OAC) prophylaxis was started between the second and third postoperative days, after drains were removed as per patient clinical condition. LMWH was administered until the patient's international normalized ratio (INR) was within a therapeutic range (2–3 after aortic valve replacement, 2.5–3.5 after mitral or tricuspid valve replacement).

Early antiplatelet prophylaxis with acetylsalicylic acid (ASA; 150 mg/day) was prescribed in cases of aortic bioprosthesis implantation, starting on SVP day, always in combination with LMWH

during the early post-procedural period. In cases of concomitant atrial fibrillation. LMWH/OAC monotherapy was recommended. Combined prophylaxis of LMWH/OAC with antiplatelet therapy (ASA/ /clopidogrel) was prescribed in cases of mechanical prosthesis implantation with CABG, recently performed percutaneous coronary intervention (PCI), or known peripheral arterial disease. In cases of bleeding early after SVP, antithrombotic prophylaxis with LMWH or antiplatelet agents was started after the achievement of proper hemostasis, in accordance with the aforementioned standardized criteria.

The outcomes evaluated in this investigation were in-hospital bleeding, transfusions (packed red blood cells, platelet concentrate, or fresh frozen plasma), reoperation due to bleeding, and thromboembolic events. The risk factors evaluated in this investigation were periprocedural prophylaxis with LMWH and OAC, differing dosage of LMWH (mg/day) used before and after SVP, and timing of LMWH/OAC cessation and initiation before and after SVP (day). Additionally, the impact of procedure related parameters were assessed, such as dosage of UFH (IU) administered during the procedure, dosage of protamine at the end of SVP (mg), two subsequent ACT measurements after UFH and protamine administration, time on CPB (min), aorta clamping time (min), and arterial blood gas analyses before and after CPB. Preoperative and postoperative data were collected from patient medical history. Detailed information regarding procedures were obtained from reviews of patient medical records.

All outcomes were assessed as in-hospital events and defined according to guidelines for reporting mortality and morbidity after cardiac valve intervention with the exception of bleeding [20]. Bleeding was defined according to the universal definition of perioperative bleeding in adult cardiac surgery, including moderate, severe and massive events (class 2–4) [21]. Although transfusion and reoperation due to bleeding are components of the bleeding definition, we also adopted these variables as separate endpoints. Thromboembolic events included prosthetic valve thrombosis, pulmonary embolism, peripheral thromboembolic events, stroke or transient ischemic attack.

Statistical analysis

Categorical data are presented as numbers and percentages. Continuous data are presented as mean ± standard deviation. Comparisons were made using the χ^2 or two-sided Fisher exact test for categorical variables. Continuous data were compared using the Student t-test and Wilcoxon test, depending on their distribution as assessed by the Shapiro-Wilk test. The association between risk factors and outcomes were performed using univariate and multivariable logistic regression analysis to estimate an odds ratio (OR) and its 95% confidence interval (CI). Additionally, the impact of LMWH and OAC dosage and timing of initiation and cessation on endpoints was assessed through a receiver operating characteristic (ROC) curve and by estimating its area under the curve (AUC) and 95% CI. The optimal values for LMWH and OAC cut-off were chosen by taking into account the greatest sum of sensitivity and specificity. The predictive values of dosage and timing of LMWH/ /OAC cessation and initiation were adjusted for potential confounding variables (**Suppl. Table 1**). Laboratory parameters were assessed on the day of SVP pre-procedure. A p-value < 0.05 was considered significant. All tests were performed using MEDcalc (Medcalc Software 2014). This study was approved by the Local Ethics Committee.

Results

This study included 388 consecutive SVP patients with a mean age of 63.6 ± 12.6 years. Among the 271 (69.84%) patients who underwent SVR, 161 (62.11%) patients received a mechanical prosthesis. Mechanical prostheses were implanted in mitral and aortic position in 42 (10.82%) and 119 (30.67%) patients, respectively. The baseline characteristics of the study population and type of procedures performed are presented in Table 1.

Early bleeding occurred in 153 (39.33%) patients, being severe and massive only in 37 (9.45%) and 14 (3.61%) cases, respectively. Reoperation due to bleeding was required in 25 (6.45%) patients and was 2.5 ± 5.03 days after SVP. Transfusions were required in 203 (52.32%) patients. The first transfusion event was mainly performed during or early after SVP (0.59 ± 0.97 days). Thromboembolic events were diagnosed in only 7 (1.8%) patients — all of them were early post-procedural strokes or transient ischemic attacks. Four (1.03%) deaths occurred during hospitalization. Two of the deceased had bleeding early after SVP, although bleeding was not the cause of death for any of them. Hospitalization time ranged between 4 and 30 days (mean 7.64 ± 2.92 days), and was significantly longer in those who bled (OR 1.19; 95% CI 1.09–1.29; p = = 0.001). All procedural and in-hospital outcomes are presented in **Supplementary Table 1**. The

Table 1. Baseline clinical characteristics of study population (n = 388).

Age [year]	20–85 (63.6 ± 12.57)
≥ 65 years	224 (57.73%)
Female sex	160 (41.23%)
NYHA class:	
I	34 (8.76%)
II	113 (29.13%)
III	225 (57.99%)
IV	16 (4.12%)
Coronary artery disease*	177 (45.62%)
Previous MI	80 (20.62%)
Previous coronary intervention:	95 (24.48%)
PCI ≤ 6 months pre-TAVI	28 (7.22%)
CABG	9 (2.32%)
COPD	25 (6.44%)
Atrial fibrillation	110 (28.35%)
Diabetes mellitus	71 (18.30%)
Hypertension	293 (75.51%)
Renal failure**	27 (6.96%)
Liver failure	19 (4.90%)
History of bleeding	48 (12.37%)
Heart failure***	253 (65.21%)
Previous stroke/TIA	25 (6.44%)
Laboratory parameters before procedure:	
Hemoglobin [g/dL]	7.4–19 (13.78 ± 1.68)
Platelet count [/μL]	114–572 (206 ± 68)
INR	0.83–1.8 (1.03 ± 0.14)
APTT	20.8–77.7 (31.06 ± 6.16)
GFR [mL/min/1.73 m^2]	22.78–76.6 (49.54 ± 21.9)
Creatinine [mg/dL]	0.52–2.35 (1.15 ± 2.75)
Type of the procedure:	
Multi-SVP	62 (6.70%)
AVR	75 (19.32%)
SVR + ascending aorta replacement	26 (6.7%)
SVP + CABG	53 (13.65%)
MVpl	24 (6.18%)
MVR	55 (14.17%)
TVpl	2 (0.5%)
Mechanical prosthesis:	161 (62.11%)
Mitral/Aortic	42 (10.82%)/119 (30.67%)
Biological prosthesis:	110 (28.35%)
Mitral/Aortic	30 (7.73%)/80 (20.61%)

Data are shown as means ± standard deviation or number (percentage). *Stenosis > 50%, **GFR < 60 mL/min/1.73 m^2 or ≥ 200 mmol/L, detected in consecutive, in-hospital testing, prior to TAVI, or previously diagnosed and treated chronic renal failure; ***Left ventricular ejection fraction < 60%. APTT — activated partial thromboplastin time; AVR — aortic valve replacement; CABG — coronary artery bypass grafting; COPD — chronic obstructive pulmonary disease; GFR — glomerular filtration rate; INR — international normalized ratio; multi-SVP — multiple valve procedures; MI — myocardial infarction; MVpl — mitral valve annuloplasty; MVR — mitral valve replacement; NYHA — New York heart Association; PCI — percutaneous coronary intervention; SVR + CABG — valve procedures and coronary artery bypass graft combined procedure; TAVI — transcatheter aortic valve implantation; TIA — transient ischemic attack; TVpl — tricuspid valve annuloplasty

impact of patient characteristics, type of procedure, and basic laboratory parameters on endpoints are presented in **Supplementary Table 2**. Periprocedural antithrombotic prophylaxis in the study population and its impact on outcomes is presented in Figure 1.

Acetylsalicylic acid was the most commonly used antiplatelet agent pre-procedure (44.6% of patients), and after SVP (56.7% of patients). Clopidogrel premedication was used in 36 (9.3%) patients and significantly increased the risk of reoperation due to bleeding (p = 0.04). No significant association between LMWH and OAC before SVP was found with any endpoint. Similarly, early post-procedural LMWH prophylaxis had no impact on endpoints. Post-procedural OAC prophylaxis was significantly associated with reduced risk of bleeding (p = 0.002), transfusion (p = 0.004), and reoperation due to bleeding (p = 0.029), without affecting the risk of thromboembolic events (p = 0.20). Impact of dosage and timing of initiation and cessation of LMWH/OAC on endpoints are presented in Figures 2–5.

Higher dosage of LMWH before SVP was an independent risk factor for bleeding and transfusion, with > 60 mg/day as a predictor for these events (Figs. 2, 3).

Receiving the first dose of LMWH on the day of SVP was an independent predictor of bleeding, transfusion and reoperation due to bleeding with > 40 mg/day as a predictor for these events (Figs. 2, 4).

Administration of LMWH within 24 h before SVP increased the risk of transfusion. Similarly, cessation of OAC within fewer than 7 days before SVP, increased the risk of transfusion and reoperation (Fig. 5). In line with these results, higher INR before SVP increased the risk of bleeding and transfusion (**Suppl. Table 2**). Time of LMWH initiation after SVP was significantly associated with the risk of bleeding (OR 2.110; 95% CI 1.359–3.287; p = 0.001) and blood transfusion (OR 2.504; 95% CI 1.546–4.055; p < 0.001). Similarly, time of OAC initiation after SVP was associated with risk of blood transfusion (OR 1.805; 95% CI 1.298–2.510; p < 0.001).

Various procedural parameters were also found to be relevant study endpoints.

Each additional minute on CPB significantly increased the risk of bleeding (OR 1.017; 95% CI 1.003–1.032; p = 0.02) and transfusion (OR 1.021; 95% CI 1.004–1.038; p = 0.014). Furthermore, a correlation was found between higher dose of protamine at the end of SVP and blood transfusion early after surgery (OR 1.002; 95% CI 1.0–1.004;

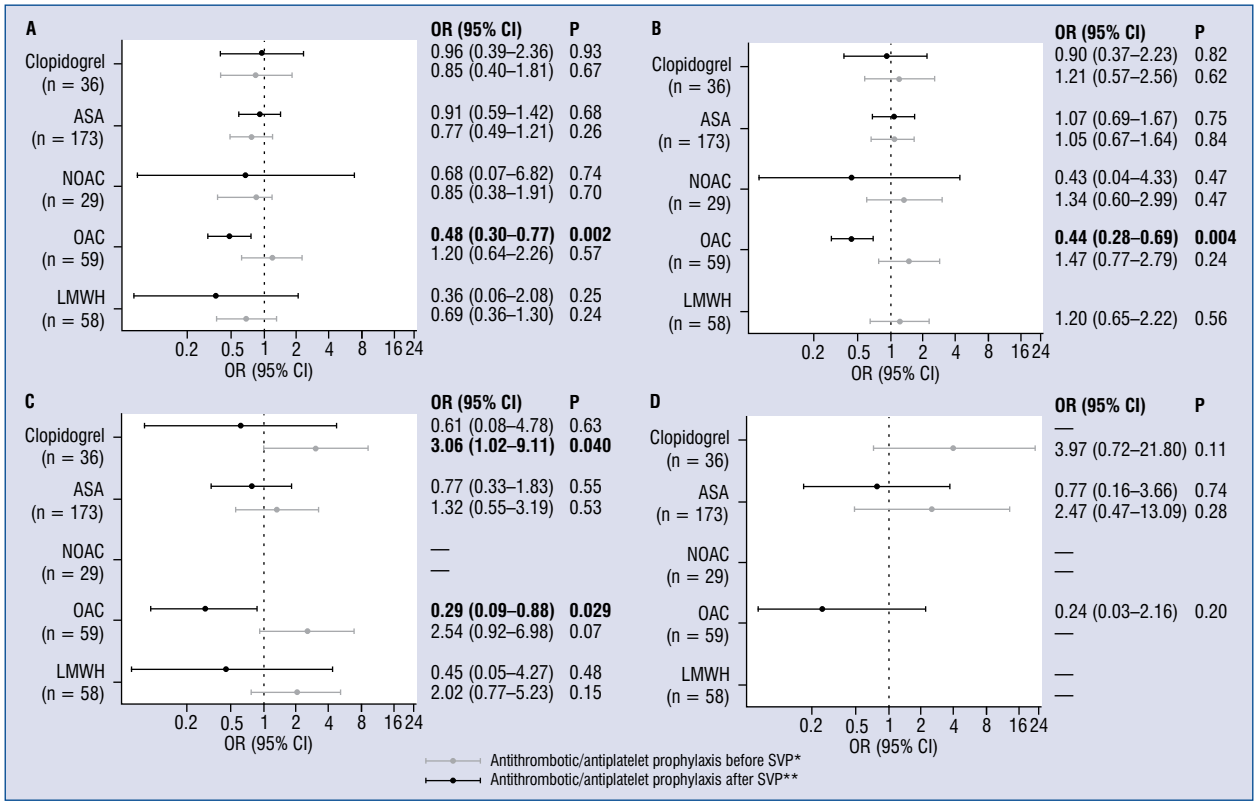

Figure 1. Impact of periprocedural antithrombotic/antiplatelet therapy on study endpoints in multivariate logistic regression analysis; **A.** Bleeding (n = 153); **B.** Transfusions (n = 203); **C.** Reoperation (n = 25); **D.** Thromboembolicevents (n = 7); *Combined therapy before SVP: dual antiplatelet therapy 15 (3.8%) patients, triple antithrombotic therapy 7 (1.8%) patients, LMWH/OAC/NOAC + ASA/clopidogrel 33 (8.5%) patients; **Combined therapy after SVP: dual antiplatelet therapy 14 (3.6%) patients, triple antithrombotic therapy 4 (1.0%) patients, LMWH/OAC/NOAC + ASA/ /clopidogrel 54 (13.9%) patients as only 7 thromboembotic events occur, we were able to produce only 4 OR in panel D; ASA — acetylsalicylic acid; CI — confidence interval; LMWH — low molecular weight heparin; NOAC — non-vitamin K antagonists oral anticoagulant; OAC — oral anticoagulation; OR — odds ratio; SVP — surgical valve procedures.

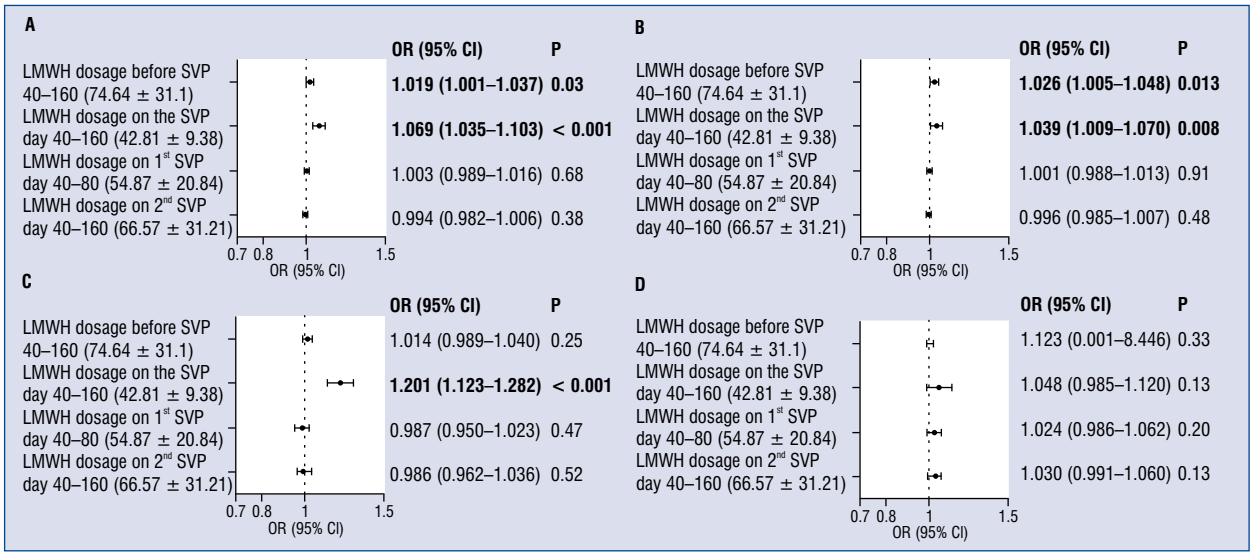

Figure 2. Impact of dosage of low molecular weight heparin (LMWH) and oral anticoagulation before and after surgical valve procedures on study endpoints in multivariate logistic regression analysis; **A.** Bleeding (n = 153); **B.** Transfusions (n = 203); **C.** Reoperation (n = 25); **D.** Thromboembolic events (n = 7). As only 7 thromboembolic events occured, the first OR in panel D for LMWH dosage before surgical valve procedures is only displayed in numbers to avoid modify the scale x axis; CI — confidence interval; OR — odds ratio.

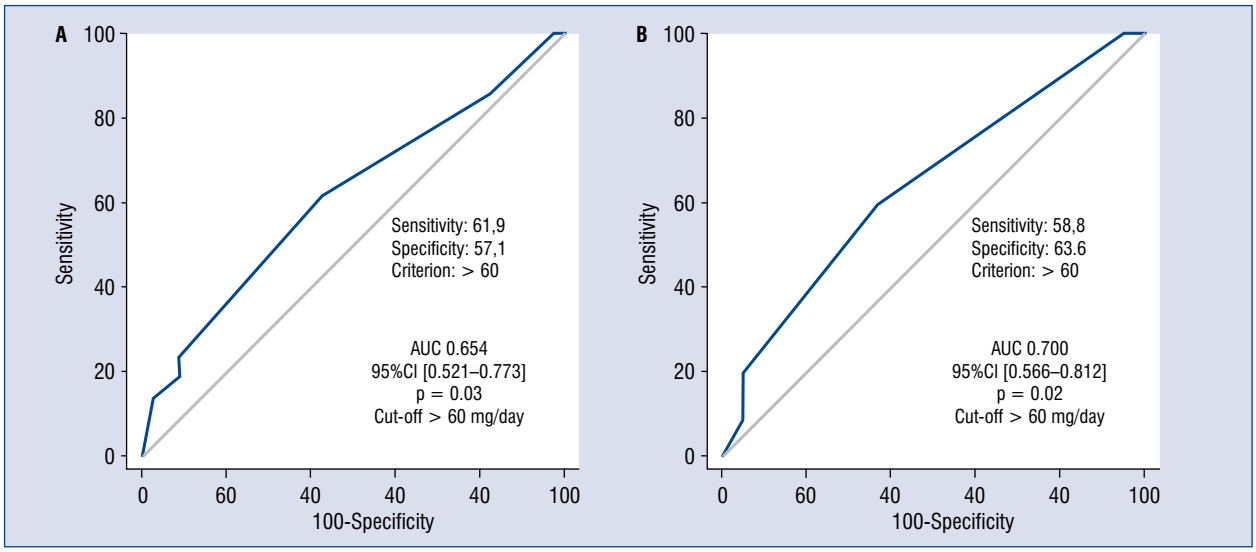

Figure 3. Impact of low molecular weight heparin (LMWH) dosage administered before surgical valve procedures on the study endpoints; **A.** Impact of LMWH dosage premedication on bleeding; **B.** Impact of LMWH dosage premedication on transfusion.

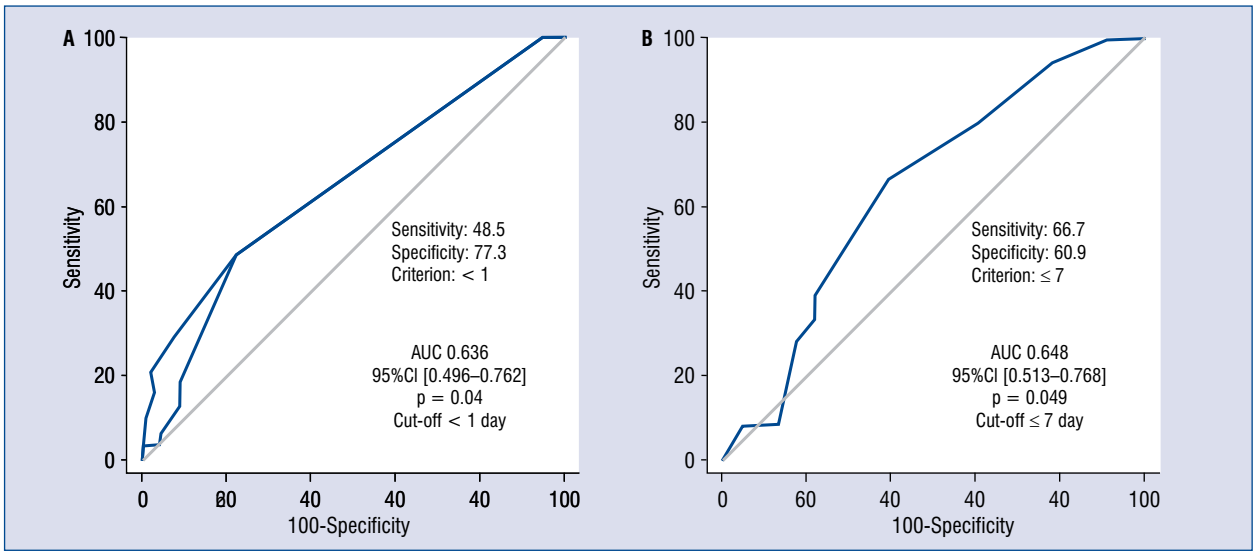

Figure 4. Impact of low molecular weight heparin (LMWH) and oral anticoagulation (OAC) time of cessation before surgical valve procedures on transfusion; **A.** Impact of LMWH cessation before SVP on transfusion; **B.** Impact the day of OAC cessation before SVP on transfusion

p = 0.04). Activated clotting time after UFH administration associated with bleeding (OR 0.997; 95% CI 0.995–0.999; p = 0.004) and thromboembolic events (OR 1.006; 95% CI 1.0–1.011; p = 0.048).

Discussion

The primary purpose of early prophylaxis after SVP is the prevention of valve thrombosis and thromboembolic events, which may be a result of temporal immobility of post-procedure patients [2, 8, 15–19]. Many experimental studies have suggested a postprocedural hypercoagulable state due to enhanced activation of plasma coagulation factors and platelets by surgically injured native heart tissue, turbulent flow across the prosthesis, and thrombogenicity of prosthesis artificial materials [1]. The necessity of chronic OAC prophylaxis

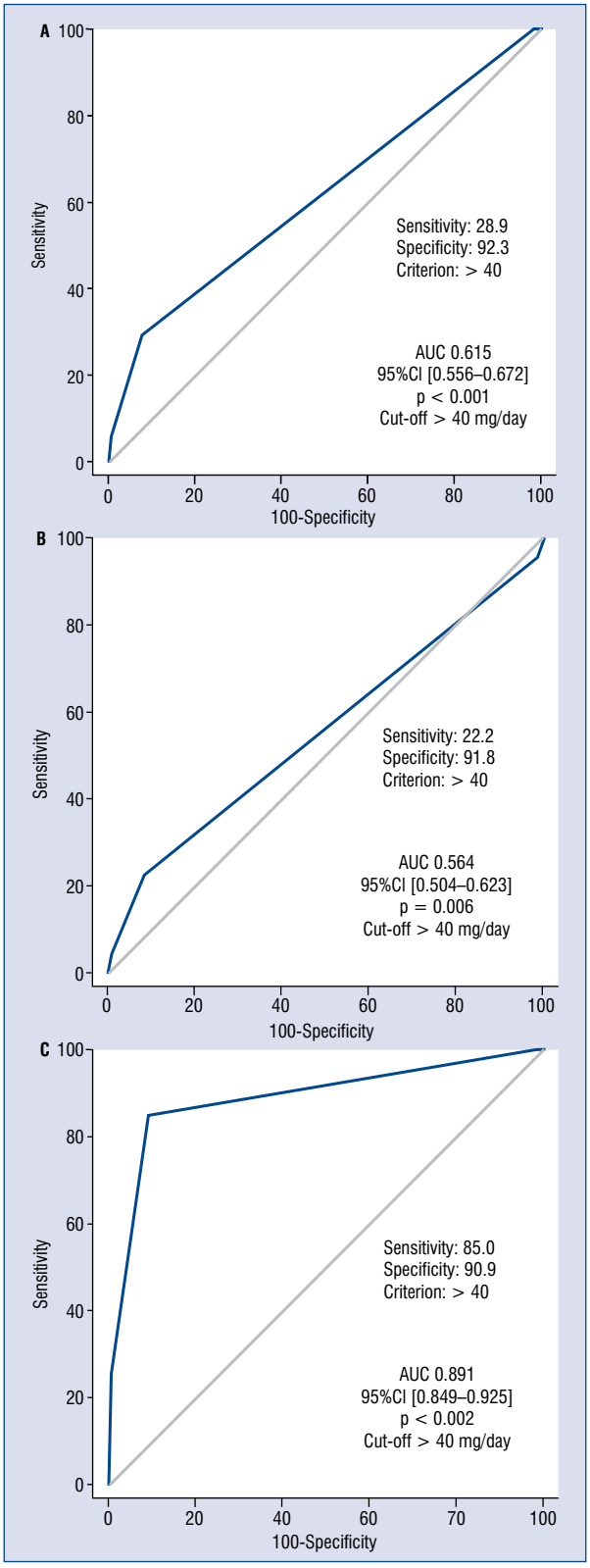

Figure 5. Impact of low molecular weight heparin (LMWH) dosage administered within 24 h after surgical valve procedures on the study endpoints; **A.** Impact of LMWH dosage on SVP day on bleeding; **B.** Impact of LMWH dosage on SVP on transfusion; **C.** Impact of LMWH dosage on SVP day on reoperation.

after SVP is well accepted. Chronic OAC provides a 75% reduction in the incidence of early thromboembolic events [1, 8, 15–19]. However, optimal prophylaxis directly after SVP remains unclear, especially when considering serious bleeding complications are among the most frequently noted in-hospital complications [1, 2, 9–12].

In this study, serious bleeding affected 13% of patients within 72 h after SVP, whereas early valve thrombosis was not observed. The only embolic events were strokes noted in fewer than 2% of subjects. These results are consistent with other studies that report bleeding occurs at least twice as often as the thromboembolic events in first 3 days after SVP, and bleeding is also the main reason for early reoperation [1, 2, 9–11, 22–24].

A variety of periprocedural antithrombic prophylaxis protocols have been proposed [1, 2, 8–11, 15–19]. Currently, the most common antithrombotic prophylaxis regimens are: early postoperative bridging with LMWH or UFH started on the day of SVP with OAC on the first postprocedural day or early OAC monotherapy with no bridging treatment [1, 2, 9, 25–29]. There is insufficient evidence to support the use of one of these strategies early after SVP [1, 2, 9–11]. Therefore, current recommendations regarding antithrombotic prophylaxis early after SVP are divergent, and a lack of consensus remains [8, 15–19].

Of note, SVP with CPB is responsible for significant consumption coagulopathy [1, 13]. Although these hemostasis disturbances are gradually restored within subsequent days, they translate into high risk of bleeding early after SVP. Considering the hemostatic disorders related to the procedure and disproportionate risk of bleeding compared to valve thrombosis, current prophylactic strategies with therapeutic doses of anticoagulants may be overly aggressive [1, 11].

Surprisingly, despite the absence of strong evidence, ESC guidelines recommend UFH bridging with early OAC implementation, and describe LMWH early after SVP as off-label prophylaxis [16]. Notably, this recommendation is based mainly on empiric, single center data [16, 29]. On the other hand, other guidelines and a substantial number of current reports suggest that LMWH after SVP is as effective as UFH and has a better safety profile than UFH, providing a rapidly achieved antithrombotic effect and predictable action without the necessity of routine laboratory monitoring [1, 9–11]. These advantages of LMWH translate into a shorter hospital stay and lower cost of hospitalization [1, 9–11].

The present study confirmed feasibility of LMWH early after SVP and described the most favorable dosage and timing of LMWH administration for optimal periprocedural prophylaxis. It was found that the most advantageous dosage of LMWH after SVP was 40–60 mg/day, which is equal to doses recommended for deep vein thrombosis prophylaxis after major surgery and for prolonged immobilization of high-risk patients [30]. Several other studies have also suggested the beneficial safety profile of prophylactic doses of heparins in comparison to therapeutic ones early after SVP, showing up to a fivefold reduction of major bleeding and a similar thromboembolic risk [1, 11].

Another insufficiently investigated concern is the safest time points for cessation and initiation of periprocedural antithrombotic prophylaxis with regard to SVP. The present results suggest that OAC should be stopped at least 6 days before SVP, while LMWH should be stopped 24 h preprocedure. These results are to some extent in agreement with guidelines that recommend stopping OAC 5 days before and LMWH between 12 and 24 h before major surgical procedures [8, 15–18].

Since this study found that dosage of LMWH on the day of SVP affected the safety outcomes, herein suggested, is the need for reassessment and special caution when considering LMWH initiation within the first 24 h of SVP. Furthermore, this especially deserves more attention given that consensus guidelines recommend considering longer delays in starting LMWH even up to 48–72 h after high bleeding risk procedures such as SVP [8, 15, 16, 18].

It is believed that the results of this study make several key contributions to the literature. Firstly, the present outcomes highlight the hemostatic profile of the SVP population in the first 72 h post-procedure, suggesting that in this period, hemostasis risk is tilted more toward bleeding than valve thrombosis. Secondly, in line with concern for increased bleeding risk, it is shown herein, that if a LMWH strategy is utilized, the most suitable approach is to use the reduced dose of LMWH as is recommended for prophylaxis of deep vein thrombosis equally before and after surgery. Similarly, as in previous studies, the present results highlight the presence of risk factors, which can modulate the safety and efficacy of antithrombotic prophylaxis. It is shown that a higher number of implanted prostheses; combined procedures, age, female sex, and New York Heart Association class of heart failure had meaningful impact on clinical endpoints. CPB time, higher value of ACT directly after UFH administration, and protamine dose with safety endpoints.

Limitations of the study

This study has several limitations. Firstly, the analysis may have limited power considering the small sample size; therefore, results should be interpreted cautiously. Secondly, the study population was heterogeneous, since it included mechanical and biological prosthesis implantation, valvuloplasty, as well as procedures combined with CABG. Additionally, the rate of bleeding was higher than expected. Although only 13% of incidents were life-threatening or severe, the rate of bleeding described in this study is substantially higher than has been previously reported [1, 2, 9–11]. This might be explained by the high surgical risk of the study population and high rate of complex procedures — 29.9% of multi-VP, 25.7% of VP+CABG, 6.7% of Bentall procedure or replacement of ascending aorta as part of a combined surgery. This might also be due to the lack of a unified definition for bleeding and thromboembolic events related to SVP. While guidelines for reporting complications during long-term follow-up after SVP exist [20], these recommendations do not address early complications during index hospitalization, such as early prosthesis thrombus, pericardial effusion, cardiac tamponade or excessive post-procedural drainage. Thus, it was elected to define early bleeding as per the most recent unified definition of perioperative bleeding from the International Initiative for Hemostasis Management in Cardiac Surgery [21]. Finally, there was an inability to thoroughly assess the impact of time of LMWH and OAC initiation after SVP. the present results are inconclusive in this regard, since time of LMWH/OAC initiation after SVP was biased by procedure related events. Although, according to the protocol, the first dose of LMWH was to be administered 8–12 h after SVP or after hemostasis achievement, no patient who experienced bleeding during SVP had LMWH started within 48 h. Since early post-procedural prophylaxis was withheld in cases of procedure related bleeding, it was difficult to determine optimal time for LMWH/OAC initiation after SVP from this data. Future studies should seek to address these limitations in a larger, carefully selected patient population.

Conclusions

Bleeding complications are the major early clinical adverse events after surgical valve pro-

cedures. Safety and efficacy of LMWH periprocedural prophylaxis depends on dosage and time of its administration. The most optimal strategy for periprocedural antithrombotic prophylaxis in the SVP population appears to be LMWH at a dosage of 40–60 mg/day, in line with what is recommended for deep vein thrombosis prophylaxis, stopped at least one day prior to the procedure.

Conflict of interest: None declared

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ORIGINAL ARTICLE

Peak systolic velocity of tricuspid annulus is inferior to tricuspid annular plane systolic excursion for 30 days prediction of adverse outcome in acute pulmonary embolism

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Abstract

Background: *Tricuspid annular plane systolic excursion (TAPSE) is an established index of right ventricular (RV) systolic function and a significant predictor in normotensive patients with pulmonary embolism (PE). Recently, Doppler tissue imaging-derived tricuspid annular systolic velocity (TV S'), a modern parameter of RV function was reported to be useful in the diagnosis and prognosis of a broad spectrum of heart diseases. Therefore, herein, is an analysis of the prognostic value of both parameters in normotensive PE patients.*

Methods: *One hundred and thirty nine consecutive PE patients (76 female, age 56.4 ± 19.5 years) were included in this study. All patients were initially anticoagulated. Transthoracic echocardiography was performed on admission. The study endpoint (SE) was defined as PE-related 30-day mortality and/or need for rescue thrombolysis.*

Results. *Seven (5%) patients who met the criteria for SE presented more severe RV dysfunction at echocardiography. Univariable Cox regression analysis showed that RV/LV ratio predicted SE with hazard risk (HR) 10.6 (1.4–80.0; $p = 0.02$); TAPSE and TV S' showed HR 0.77 (0.67–0.89), $p < 0.001$, and 0.71 (0.52–0.97), $p = 0.03$, respectively. Area under the curve for TAPSE in the prediction of SE was 0.881; 95% CI 0.812–0.932, $p = 0.0001$, for TV S' was 0.751; 95% CI 0.670–0.820, $p = 0.001$. Multivariable analysis showed that the optimal prediction model included TAPSE and systolic blood pressure (SBP showed HR 0.89 95% CI 0.83–0.95, $p < 0.001$ and TAPSE HR 0.67, 95% CI 0.52–0.87, $p<0.03$). Kaplan-Meier analysis showed that initially PE patients with TAPSE ≥ 18 mm had a much more favorable prognosis that patients with TAPSE < 18 mm ($p < 0.01$), while analysis of S' was only of borderline statistical significance.*

Conclusions: *It seems that TV S' is inferior to TAPSE for 30 day prediction of adverse outcome in acute pulmonary embolism.* (Cardiol J 2020; 27, 5: 558–565)

Key words: transthoracic echocardiography, right ventricular function, tricuspid valve, Doppler tissue imaging, prognosis, pulmonary embolism

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Introduction

Normotensive patients with acute pulmonary embolism (PE) include not only subjects with a benign clinical course, but also patients with an increased risk of PE-related mortality. Intermediate-high-risk PE patients require close monitoring to detect hemodynamic decompensation and to consider rescue reperfusion therapy [1].

Right ventricular dysfunction (RVD) detected at computed tomography or in transthoracic echocardiography (TTE) indicates an increased risk of a complicated clinical course, including early mortality. The assessment of right ventricle (RV) function is recommended in the current 2014 guidelines of the European Society of Cardiology (ESC) for risk stratification of normotensive PE patients [1, 2]. However, despite accumulating evidence there is generally no accepted echocardiographic definition of RVD proposed for risk stratification in normotensive PE patients. The criteria used to define RVD vary between studies and have included RV dilatation, an increased RV/LV diameter ratio, hypokinesis of the free RV wall, an increased velocity of the tricuspid regurgitation jet [1–4]. As shown previously, that in initially normotensive PE patients tricuspid annular plane systolic excursion (TAPSE), the only independent echocardiographic outcome predictor among a wide set of echocardiographic indices [5], and others subsequently reported similar results [6].

Doppler tissue imaging (DTI) has become a widely available technique, which plays an important role in the diagnosis and prognosis of a broad spectrum of heart diseases [7–9]. It is a simple, reproducible diagnostic method with a good ability to detect RV dysfunction [10]. DTI-derived tricuspid lateral annular systolic velocity (TV S') correlates well with other parameters of global RV systolic function [11, 12]. It was reported that the assessment of RV myocardial S' velocity by DTI may be adequate to confirm RVD in patients with PE [13, 14]. DTI can be also used to monitor RV function and filling pressure in PE patients [15].

Although there are some reports suggesting a prognostic value of TV S' in patients with acute PE [16, 17], no direct comparison between TAPSE and tricuspid annular systolic velocity (TV S') is available. Therefore, the prognostic value of both parameters in normotensive PE patients was analyzed.

Methods

Patients and management of acute PE

The study group comprised of consecutive patients with symptomatic PE managed in the documented department. All cases were hemodynamically stable at admission, with systemic systolic blood pressure (SBP) exceeding 90 mmHg, and no signs of peripheral hypoperfusion. Pulmonary embolism was confirmed by contrast-enhanced multi-detector computed tomography when thromboemboli were visualized at least at the level of segmental pulmonary arteries. Acute PE was diagnosed when symptoms of PE had been present for no longer than 14 days before the diagnosis.

All patients were initially anticoagulated with body mass adjusted low molecular weight heparin or activated partial thromboplastin time adjusted unfractionated heparin infusion. In the case of clinical deterioration, urgent rescue thrombolysis (rtPA 0.6 mg/kg body weight, max 50 mg i.v.) was performed. Hemodynamic deterioration was defined by systemic hypotension < 90 mmHg with signs of peripheral hypoperfusion, with tachycardia exceeding 110 bpm. A decision to escalate treatment was facilitated by significant dyspnea. Oral anticoagulation preferably with non-vitamin K antagonist oral anticoagulants or with international normalized ratio adjusted vitamin K antagonists were started according to the decision of the managing physician.

Comorbidities were defined as presence of chronic obstructive pulmonary disease (COPD), chronic heart failure (CHF) or active cancer.

Patients not included were those with severe tricuspid regurgitation, a history of RV myocardial infarction, after tricuspid valve replacement, or those with confirmed chronic thromboembolic pulmonary hypertension.

Echocardiography

Standardized transthoracic echocardiography focused on the assessment of RV function was performed using Philips iE33 (Philips Medical Systems, Andover, Massachusetts) and Philips Epiq 7 systems (Philips Medical Systems, Best, the Netherlands) according to the previously described protocol [18], as soon as possible after admission.

Briefly, left ventricle and right ventricle diameters were measured in the apical four chamber view (LV4C, RV4C, respectively) at the level of the mitral and tricuspid valve tips at end-diastole (defined by the ECG R wave). The presence of the McConnell sign was assessed [19]. TAPSE was measured using M-mode presentation in the

apical 4-chamber view, with the cursor exactly aligned along the direction of the tricuspid lateral annulus [11].

Peak systolic velocity of the lateral part of the tricuspid annulus — TV S' was measured using DTI. Sample volume of pulsed DTI was placed in the tricuspid annulus or in the middle of the basal segment of the RV free wall. To achieve a high quality of recording optimal gain was used. The TV S' velocity was defined as the highest systolic velocity, without over gaining the Doppler envelope [10, 11]. The isovolumic contraction velocities were excluded from the TV S' measurement.

In the parasternal short axis view, flattening of the interventricular septum was assessed qualitatively, and the acceleration time (AcT) of pulmonary ejection was measured in the right ventricle outflow tract, proximally to the pulmonary valve (PW Doppler).

Tricuspid regurgitation peak systolic gradient (TRPG) was calculated by the simplified Bernoulli formula using tricuspid regurgitant flow peak velocity (Doppler continous wave). The examination was completed by the measurement of the inferior vena cava (IVC) at late expiration.

Left ventricular ejection fraction (LVEF) was measured with the modified biplane Simpson method [11]. Doppler measurements reflected an average of three cardiac cycles. The inter- and intra-observer agreement for echocardiographic parameters were previously published [18].

Examinations were digitally recorded and interpreted by experienced sonographers according to a standardized protocol following recommendations of the European Association of Cardiovascular Imaging [11].

In 117 patients TTE was performed within the first 24 h after admission, while in 22 patients, this examination was performed between 24 and 72 h after admission.

Study endpoint

The study endpoint was a combination of 30-day PE-related mortality or need for rescue thrombolysis or both in patients with hemodynamic deterioration.

Statistical analysis

Data characterized by a normal distribution are expressed as mean followed by standard deviation. Parameters without such a distribution are expressed as median with range. The Student t-test or Mann-Whitney U-test was used for comparisons between the two groups. The chi-square/chi-squared test was used to compare discrete variables (with the Yates correction when needed). Receiver operating characteristics (ROC) analysis was performed and the area under the curve (AUC) was determined to test the performance of selected echocardiographic parameters with regard to the prediction of serious adverse event (SAE). Youden's index quantification was used to identify optimal cohort-specific cut-off values. The impact of TAPSE and S' on study end points was evaluated using univariable Cox proportional-hazards regression. Hazard risk (HR) and corresponding 95% confidence intervals (CI) were calculated. Kaplan-Meier analysis was used to investigate cumulative 30-day event free survival rate. Forward stepwise selection with a 0.1 level for staying in the model was used to identify significant predictors in multivariable analysis. Areas under ROC curves were compared pair-wise. Sensitivity, specificity, negative predictive values (NPV), positive predictive values (PPV), and the corresponding 95% CI were calculated for TAPSE and TV S'. All tests were two-sided. Data were considered significant at $p < 0.05$. STATISTICA data analysis software system (StatSoft, Inc. 2011, version 10, www.statsoft.com) and MedCalc® software (version 11.0.0.0) were used for statistical calculations. This observational study was approved by the local Ethics Committee.

Results

Patients characteristics and clinical course

The study included 139 consecutive patients with PE (63 males, 76 females, age 56.4 ± 19.5 years), normotensive at admission. The study outcome defined as 30-day PE-related mortality and/or need for rescue thrombolysis in patients with hemodynamic deterioration was observed in 7 (5%) of the patients studied. Despite anticoagulation 6 (4.3%) patients experienced hemodynamic collapse and underwent rescue thrombolysis, 4 of them survived. 30-day PE-related mortality was 2.2% (3 patients), and all-cause mortality was 2.9% (4 patients). The one none-PE related death occurred in a 92-year-old patient with metastatic cancer. Initial systemic SBP was significantly lower in patients who experienced serious adverse events (SAE (+)) than in patients with an uncomplicated clinical course (SAE (–)). There was no difference in age and heart rate between SAE (+) and SAE (–) groups. Clinical characteristics of patients studied are presented in Table 1.

Table 1. Clinical characteristics of 139 normotensive patients with pulmonary embolism (PE).

Parameter	All patients (n = 139)	SAE (+) (n = 7)	SAE (–) (n = 132)	P
Female/male	76/63	5/2	71/61	0.9
Age [years]	56.4 ± 19.5	61.6 ± 19.9	56.1 ± 19.6	0.5
Systemic systolic BP [mmHg]	130 ± 21.4	100 ± 11.5	131.6 ± 20.5	**0.001**
Heat rate [1/s]	90.6 ± 18.7	106.3 ± 22.7	89.8 ± 18.2	0.1
Comorbidities (COPD, CHF, neoplasm) [%]	9	1 (16.7)	26 (19.5)	0.8
Rescue thrombolysis [%]	6 (4.3)	6 (85.7)	0	–
PE-related death/all cause death	3/4	3/0	0/1	–

Data are expressed as mean ± standard deviation, median and range, or percentage. BP — blood pressure; CHF — chronic heart failure; COPD — chronic obstructive pulmonary disease; SAE — serious adverse event

Table 2. Echocardiographic characteristics of 139 initially normotensive pulmonary embolism patients.

Parameter	All patients (n = 139)	SAE (+) (n = 7)	SAE (–) (n = 132)	P
RV4C [mm]	38.8 ± 7.7	43.3 ± 7.5	38.6± 7.7	0.2
LV4C [mm]	40.5 ± 6.4	32.5 (26–54)	40.7 ± 6.0	0.35
RV/LV4C	1.0 ± 0.3	1.3 ± 0.4	1.0 ± 0.3	0.12
AcT [ms]	80 (37–166)	61.3 ± 14.6	81 (42-165)	**< 0.016**
TRPG [mmHg]	33 (10–106)	46.5 ± 7.2	32 (15–57)	**0.01**
TAPSE [mm]	20 ± 5	14± 4	21 ± 5	**< 0.001**
TV S' [cm/s]	13.0 (6.3–25.7)	10.2 (6.3–12.3)	13.9 (6.6–25.7)	**0.03**
IVS flattening [%]	39 (28)	4 (57)	35 (26.5)	0.4
McConnell sign [%]	39 (28)	4 (57)	35 (26.5)	0.4
IVC [mm]	14 (5–30)	19.2 ± 4.0	14 (5-30)	**0.005**
LVEF [%]	59.5 ± 6.2	55 (30–60)	60.4 ± 5.6	0.1

Data are expressed as mean ± standard deviation, median and range or percentage. RV4C — right ventricular dimension in apical four chamber view; LV4C — left ventricular dimension in apical four chamber view, RV/LV 4C — right ventricle to left ventricle ratio in the apical four chamber view; AcT — pulmonary ejection acceleration time, TRPG — tricuspid regurgitation peak gradient; TAPSE — tricuspid annular systolic plane excursion; TV S' — peak systolic velocity of lateral part of tricuspid annulus; IVS — interventricular septum; IVC — inferior vena cava; LVEF — left ventricular ejection fraction; SAE — serious adverse event

Echocardiography

Echocardiographic data of the group studied are included in Table 2. Patients with a complicated clinical outcome presented more pronounced echocardiographic signs of RVD. Mean values of TAPSE and TV S' (Figs. 1, 2) and AcT were significantly lower, while TRPG and IVC were significantly higher in the SAE (+) group when compared with the SAE (–) group.

The McConnell sign and flattening of IVS were more frequent in SAE (+) patients, but without statistical significance. There were no differences in RV4C dimensions, RV/LV ratio, and LVEF between SAE (+) and SAE (–) groups.

Echocardiographic predictors of clinical endpoint

Univariable Cox proportional-hazards regression analysis showed that several echocardiographic parameters significantly predicted a complicated clinical outcome. Importantly, TAPSE and TV S' showed similar HRs, HR 0.77 (0.67–0.89), $p < 0.001$, and 0.71 (0.52–0.97), $p = 0.03$, respectively (Table 3).

ROC curve analysis

ROC analysis showed that the AUC for TAPSE in the prediction of a complicated clinical course was 0.881, 95% CI 0.812–0.932, $p = 0.0001$, mean-

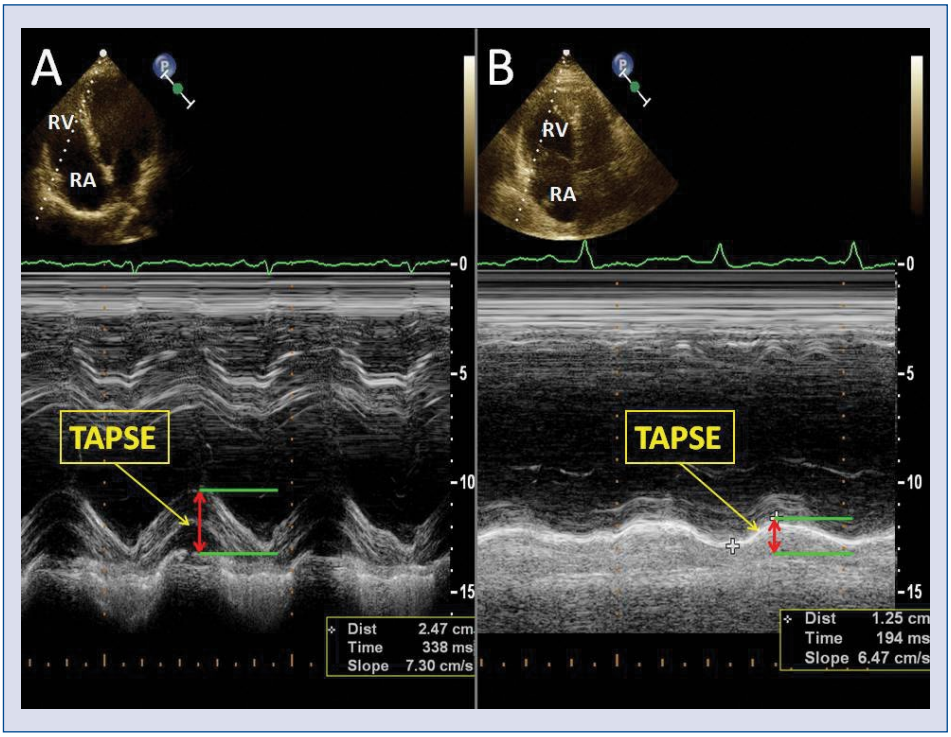

Figure 1. M-mode presentation of tricuspid annular plane systolic excursion (TAPSE) in two initially normotensive patients with acute pulmonary embolism; **A.** Patient with a benign clinical course (distance 25 mm — red double-headed arrow); **B.** Patient with a complicated clinical outcome and decreased annular movement (distance 12.5 mm — red double-headed arrow); RA — right atrium; RV — right ventricle.

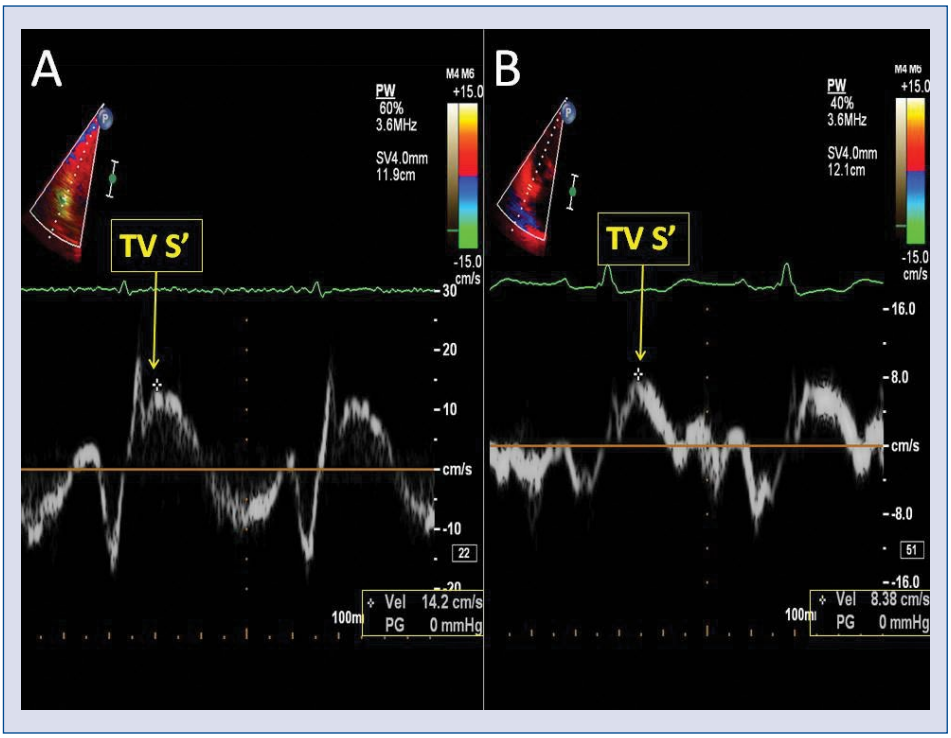

Figure 2. Tissue Doppler of the tricuspid annulus in two initially normotensive patients with acute pulmonary embolism; **A.** Patient with a benign clinical course (TV S′ 14.2 cm/s — yellow arrow); **B.** Patient with a complicated clinical outcome and decreased annular velocity (TV S′ 8.4 cm/s — yellow arrow); TV S′ — peak systolic velocity of lateral part of tricuspid annulus.

Table 3. Univariable echocardiographic predictors of pulmonary embolism-related mortality or rescue thrombolysis in 139 initially normotensive patients.

Parameter	HR	95% CI	P
TAPSE [mm]	0.77	0.67–0.89	**< 0.001**
TV S' [cm/s]	0.71	0.52–0.97	**0.03**
TV S' ≤ 12.3 [cm/s]	4.3	0.8–22.3	**0.08**
AcT [ms]	0.96	0.91–1.00	0.06
TRPG [mmHg]	1.03	0.99–1.07	0.14
IVC [mm]	0.14	0.99–1.07	0.057
RV/LV	10.6	1.4–80.0	0.02

TVS' < 12.3 cm/s was defined using receiver operating characteristics analysis. TAPSE — tricuspid annular systolic plane excursion; TV S'— peak systolic velocity of lateral part of tricuspid annulus; AcT — pulmonary ejection acceleration time; TRPG — tricuspid regurgitation peak gradient; IVC — inferior vena cava; RV/LV — right ventricle to left ventricle ratio; OR — odds ratio; CI — confidence interval

Table 4. Sensitivity and specificity of receiver operating characteristics derived cut-offs of tricuspid annular systolic plane excursion (TAPSE) and peak systolic velocity of lateral part of tricuspid annulus (TV S') in serious adverse event prediction.

	Sensitivity	Specificity	NPV	PPV
TAPSE ≤ 18 [mm]	100%	68%	100%	16%
TV S' ≤ 12.3 [cm/s]	86%	60%	99%	10%

NPV — negative predictive value; PPV — positive predictive value

while for TV S' AUC 0.751; 95% CI 0.670–0.820, p = 0.001; Fig. 3).

Importantly, a direct comparison showed that AUC for TAPSE and for TV S' did not differ significantly. Using the Youden's index, a cut-off point for TAPSE at 18 mm and for TV S' at 12.3 cm/s were identified as optimal values for SAE prediction. When cut off values of TAPSE and TVS' defined according to ROC analysis were used in hazard risk analysis TAPSE < 18 showed HR for study end point of 16.3 (2.0–135.3, p = 0.01), while TV'S < 12.3 cm/s was only of borderline significance HR 4.3 (0.8–22.2, p = 0.08).

Table 4 shows the sensitivity and specificity of ROC-derived cut-offs for TAPSE and TV S' in SAE prediction.

Multivariable analysis testing all clinical and echocardiographic parameters which were found to be significant in the univariable analysis were

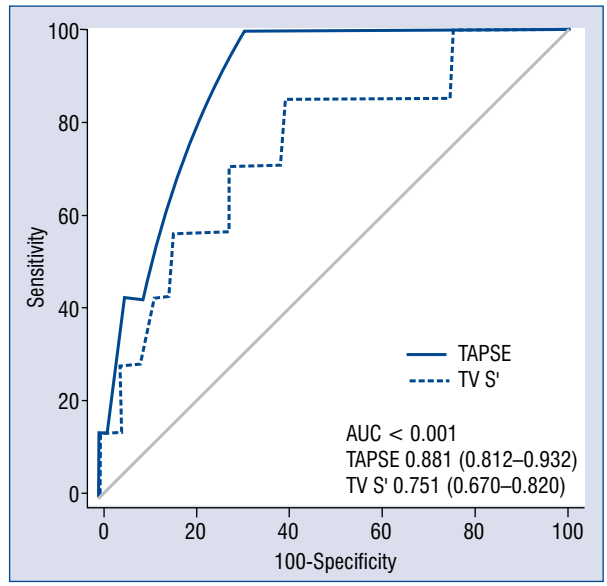

Figure 3. Receiver-operating characteristic (ROC) analysis of tricuspid annular plane systolic excursion (TAPSE) and peak systolic velocity of the lateral part of tricuspid annulus (TV S') in serious adverse event prediction in 139 normotensive pulmonary embolism patients. ROC analysis of TAPSE and TV S' for 30-day pulmonary embolism-related mortality and/or need for rescue thrombolysis in normotensive patients; AUC — area under the curve.

performed. Multivariable analysis showed that the optimal prediction model included TAPSE and systemic SBP only, while other clinical and echocardiographic parameters, with TV S' were not included. SBP showed HR 0.89 95% CI 0.83–0.95, p < 0.001 and TAPSE HR 0.67, 95% CI 0.52–0.87, p < 0.03. Kaplan-Meier analysis showed that initially PE patients with TAPSE ≥ 18 mm had much more favorable prognosis that patients with TAPSE < 18 mm (p < 0.01), while Kaplan-Meier analysis of S' was only of borderline statistical significance (Fig. 4).

Discussion

Normotensive patients with acute PE include subjects with a benign clinical course, as well as patients with an increased risk of PE-related mortality, who can deteriorate despite anticoagulation. Although short-term prognosis in acute PE predominantly depends on the hemodynamic status, RVD detected at echocardiography has significant prognostic value, especially in initially hemodynamically stable PE patients [5]. Several echocardiographic parameters for quantitative assessment of RV systolic function have been intensively studied, however echocardiographic assessment

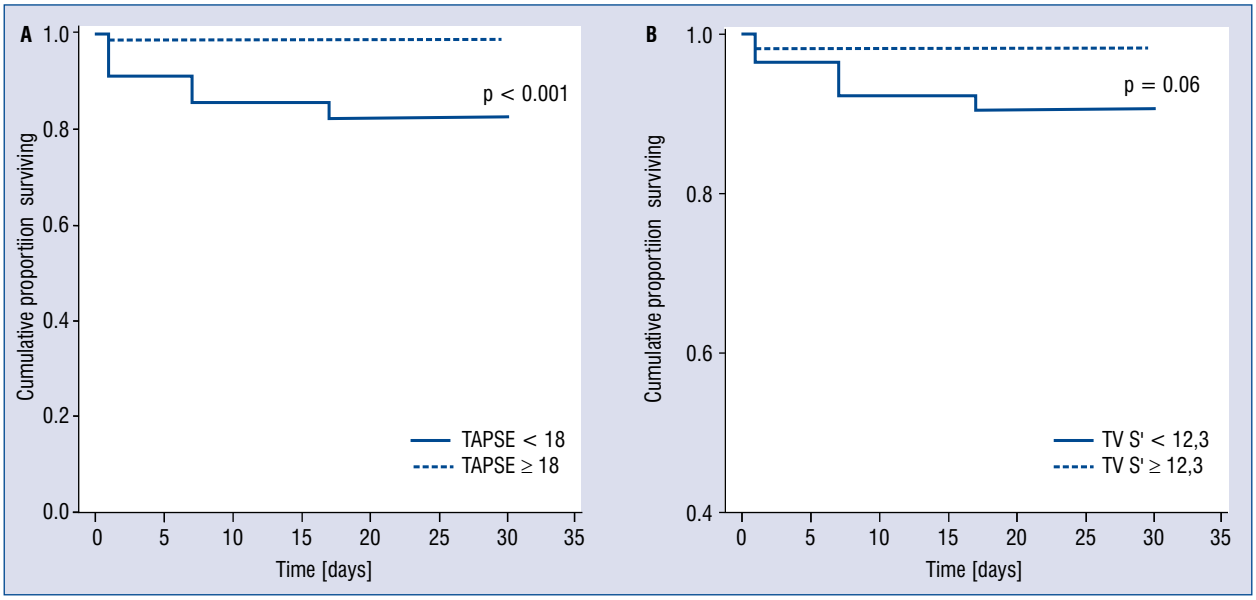

Figure 4. Kaplan-Meier analysis of tricuspid annular plane systolic excursion (TAPSE; **A**) and peak systolic velocity of lateral part of tricuspid annulus (TV S', **B**) for event free 30 day survival in 139 initially normotensive patients.

of RV function remains challenging because of the complex RV anatomy. Various echocardiographic criteria have been proposed as prognostic parameters, however decreased TAPSE was recently reported to be superior to other indices including RV/LV ratio or TRPG [5, 6].

There is accumulating evidence that tricuspid valve systolic velocity assessed with tissue Doppler is a significant prognostic parameter in various diseases affecting RV [20]. Moreover, the assessment of RVD with tissue Doppler was reported to be related to pulmonary artery thromboembolic burden. Mid-right ventricular myocardial longitudinal dysfunction quantified by tissue Doppler was related to the degree of pulmonary vascular obstruction [21]. Since tissue Doppler has become widely available and the measurement of peak systolic velocity of tricuspid annulus can be performed easily, which were compared herein, the two parameters of RV systolic function, TAPSE or TV S', was more useful in the prognosis assessment in initially hemodynamically stable patients with acute PE. A univariable analysis revealed that both indices significantly predicted a complicated clinical outcome, defined by hemodynamic collapse and need for rescue thrombolysis or PE-related 30-day mortality or both. Additionally, TAPSE and TV S' were characterized by a high AUC in ROC analysis (AUC 0.881; 95% CI 0.812–0.932 p = 0.0001; and AUC 0.751; 95% CI 0.670–0.820, p = 0.001, respectively). Furthermore, Youden's index was used to determine optimal predictive values for both parameters. In the group of 139 consecutive PE patients there were 7 SAE cases including 3 PE related deaths. TV S' < 12.3 cm/s was characterized by HR of 4.3, 95% CI 0.8–22.3, p = 0.08 for complicated clinical course and showed 86% sensitivity and 60% specificity in SAE prediction. However, when all significant clinical and echocardiographic parameters were included in the multivariable analysis only systemic SBP and TAPSE were found to be of predictive value. Thus, it seems that TV S' is not superior to TAPSE in early risk stratification in normotensive patients with acute PE. The present data corresponds with a recent observation that TAPSE is a reliable predictor of RV systolic dysfunction, and that TAPSE can be recommended for clinical use [22]. Interestingly, no significant differences were found in the initial values of TAPSE or TV S' between patients who died 1 year after discharge and patients who are still alive.

Limitations of the study

The main limitation of the current study is its single center character with a relatively small number of patients studied and a low number of clinical end points. Therefore, the results of the current study should be interpreted with caution.

Additionally, the DTI measurement is angle-dependent and both TAPSE and TV S' measurements are influenced by movement of the whole heart.

Conclusions

Although TV S' predicts short term outcome in normotensive patients with acute symptomatic PE, it seems to be inferior to TAPSE for 30 day prediction of adverse outcome and therefore TAPSE should be recommended as part of the echocardiographic assessment in this group of patients.

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Conflict of interest: None declared

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The Silesian Registry of Out-of-Hospital Cardiac Arrest: Study design and results of a three-month pilot study

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Abstract

Background: *Despite the introduction of the concept known as "Chain of Survival" has significantly increased survival rates in patients with out-of-hospital cardiac arrest (OHCA), short-term mortality in this group of patients is still very high. Epidemiological data on OHCA in Poland are limited. The aim of this study was to create a prospective registry on OHCA covering a population of 2.7 million inhabitants of Upper Silesia in Poland. Presented herein is the study design and results of a 3-month pilot study.*

Methods: *The Silesian Registry of Out-of-Hospital Cardiac Arrest (SIL-OHCA) is a prospective, population-based registry of OHCA, of minimum duration which was planned for 12 months; from January 1st, 2018 to December 31st, 2018. The first 3 months of the study constituted the pilot phase. The inclusion criterion is the occurrence of OHCA in the course of activity of the Voivodeship Rescue Service in Katowice, Poland.*

Results: *During the 3-month pilot phase of the study there were 390 cases of OHCA in which cardiopulmonary resuscitation was undertaken. Estimated frequency of OHCA in the population analyzed was 57 per 100,000 population per year. Shockable rhythm was present in 25.8% of cases. Return of spontaneous circulation was achieved in 35.1% of the whole cohort. 28.7% of patients were admitted to the hospital, including 2.8% of patients, who were admitted during an ongoing cardiopulmonary resuscitation.*

Conclusions: *Prehospital survival of patients with OHCA in Poland is still unsatisfactory. It is believed that data collected in SIL-OHCA registry will allow identification factors, which require improvement in order to reduce short- and long-term mortality of patients with OHCA.* (Cardiol J 2020; 27, 5: 566–574)

Key words: out-of-hospital cardiac arrest, cardiopulmonary resuscitation, emergency medical services, registry

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Table 1. Questions to be answered by the results of Silesian Registry of Out-of-Hospital Cardiac Arrest.

What is the frequency of OHCA in the Polish population?
What is the frequency of ROSC?
Which factors may affect the occurrence of ROSC?
What percentage of OHCA patients survive until admission to hospital?
What is the in-hospital/30-day mortality of patients with ROSC?
What percentage of patients who survive beyond 12 months after OHCA?
What factors affect the prognosis in patients with OHCA?
What is the percentage of OHCA patients whose primary cause of OHCA is cardiovascular disease?
What percentage of patients undergo coronary angiography/percutaneous coronary intervention during the first hospitalization after OHCA?
What percentage of patients with OHCA undergo implantable cardioverter-defibrillator implantation during the first year after OHCA?
What percentage of patients with OHCA undergo cardiological/neurological rehabilitation within a year after OHCA?

OHCA — out-of-hospital cardiac arrest; ROSC — return of spontaneous circulation

Introduction

Cardiovascular diseases are both the leading cause of death in adults of developed countries, and the most frequent cause of out-of-hospital cardiac arrest (OHCA) [1–5]. The introduction of the concept known as "chain of survival" has significantly increased the survival rate of patients with OHCA [4]. Nonetheless the mortality in this group of patients is still very high, and less than 10% of patients survive until hospital discharge [2]. Epidemiological data concerning OHCA in the European population is mainly provided from prospective registries, which number has increased over the last several years [3, 6–9]. Nonetheless, data on OHCA in Poland remains limited. The aim herein, therefore, was to create the Silesian Registry of Out-of-Hospital Cardiac Arrest (SIL-OHCA; ClinicalTrials.gov Identifier: NCT03654859) which covers a population of 2.7 million inhabitants of Upper Silesia. Main goals of SIL-OHCA are presented in Table 1. The study design of SIL-OHCA and the results of a 3-month pilot study are presented in this paper.

Methods

SIL-OHCA is prospective, population-based registry of OHCA, a minimum duration was planned for 12 months, from January 1st, 2018 to December 31st, 2018 with the possibility of prolonging the study period. The first 3 months of the study (1st January 2018 to 30th March 2018) constituted the pilot phase. The area covered by the registry is a part of the Silesian Voivodeship (3883 km^2, 1.2% of the total area of Poland), this corresponds to the region of activity of the Voivodeship Rescue Service in Katowice. There are 2,700,000 inhabitants in the area covered by this registry (7% of the population of Poland) and the mean population density is 695 persons per km^2. Voivodeship Rescue Service in Katowice is the biggest public, emergency medical services (EMS) provider in Poland and is the sole EMS provider in the area covered by SIL-OHCA registry, excluding Polish Medical Air Rescue. There are 88 EMS ambulances in the structures of Voivodeship Rescue Service in Katowice, including 66 ambulances, consisting of two paramedics, and 22 ambulances, consisting of two paramedics and a physician. On average the number of EMS responses of Voivodeship Rescue Service in Katowice is 250,000 per year. Voivodeship Rescue Service in Katowice follows cardiopulmonary resuscitation (CPR) algorithms based on European Resuscitation Council guidelines [10, 11].

From 1st January to 30th June 2018 (including the pilot phase of the study) all cases of OHCA with CPR started or continued by EMS and cases with confirmed OHCA and the return of spontaneous circulation (ROSC) before EMS arrival have been included in the study (regardless of the cause of OHCA and age of patients). Additionally, starting from 1st July 2018 all OHCA cases where resuscitation was not attempted have been included as well.

All EMS of Voivodeship Rescue Service in Katowice are required to fill out a standardized, paper-based questionnaire, immediately after completing medical activities. The questionnaire template is presented in Figure 1. In the case of intervention of more than one EMS, data provided

A

Silesian Registry of Out-of-Hospital Cardiac Arrest – Questionnaire template valid from 1st July 2018. Please fill out this questionnaire in every case of out-of-hospital cardiac arrest, regardless of whether CPR is attempted. *Abbreviations: EMS – emergency medical service; CRT-P - implantable cardiac resynchronization therapy pacemaker; CRT-D - cardiac resynchronization therapy defibrillator; ICD - implantable cardioverter defibrillator; ROSC - return of spontaneous circulation.*

<table>
<tr><td rowspan="3">A</td><td colspan="2">Date of birth (yyyy.mm.dd) □□□□.□□.□□</td><td colspan="2">Age (only if date of birth is unknown) □□□ years.</td></tr>
<tr><td>Number of intervention: □□□□□□□□□□</td><td>Type of EMS: S □ / P □</td><td>Sex: M □ /F □</td><td>Date/hour of receiving call (yyyy.mm.dd)/(hh:mm): □□□□.□□.□□ / □□:□□</td></tr>
<tr><td colspan="3">Did the dispatcher identify presence of cardiac arrest: Yes □ / No □</td><td>Time of arrival of the first EMS to the scene (hh:mm): □□:□□</td></tr>
<tr><td rowspan="4">B</td><td colspan="4">EMS witnessed cardiac arrest?: Yes □ / No □ (if YES, pleas skip to part C)</td></tr>
<tr><td colspan="4">Bystander witnessed cardiac arrest (collapse)? (other persons than EMS): Yes □ / No □</td></tr>
<tr><td colspan="4">Did the dispatcher provide telephone CPR instructions to the caller? Yes □ / No □</td></tr>
<tr><td colspan="2">Did bystanders perform CPR before EMS arrival?: Yes □ / No □</td><td colspan="2">If YES what were they doing?:
Compression only □ /
Compression + ventilations □

Did bystanders use AED?:
No □ / Yes, shock not delivered □ / Yes, shock delivered □</td></tr>
<tr><td rowspan="8">C</td><td colspan="4">Approximate time of cardiac arrest (yyyy.mm.dd)/(hh:mm) □□□□.□□.□□ / □□:□□</td></tr>
<tr><td colspan="4">Arrest location: home or residence □ / workplace □ / recreation event □ / street/highway □ / public building □ / educational institution □ / nursing home □ / GP surgery □ / other □</td></tr>
<tr><td colspan="4">Aetiology of cardiac arrest: medical (presumed cardiac, other medical, or unknown) □ / traumatic □ / drug overdose (medications, recreational drugs, ethanol or other) □ / drowning □ / electrocution □ / asphyxial (external causes of asphyxia, such as foreign-body airway obstruction, hanging, or strangulation) □</td></tr>
<tr><td colspan="4">Source of information on medical history: family □ / other witness □ / medical records □ / medical history unavailable □</td></tr>
<tr><td colspan="4">Comorbidities: previous myocardial infarction □ / coronary artery disease (previous PCI or CABG) □ / previous stroke □ / diabetes □ / malignancies □ / other □ (which?)……</td></tr>
<tr><td colspan="4">Implanted device: pacemaker or CRT-P □ / ICD or CRT-D □ / left ventricular assist device (heart pump) □</td></tr>
<tr><td colspan="4">Symptoms preceding cardiac arrest: none □ / dyspnoea □ / chest pain □ / abdominal pain □ / swelling □ / weakness □ / excitation □ / neurological symptoms □ / other □ (which?)……</td></tr>
<tr><td colspan="4">Duration of symptoms prior to cardiac arrest: unknown □ / less than 10min □ / less than 30min □ / less than 1h □ / 1-24h □ / over 24h □</td></tr>
<tr><td colspan="4">Was the patient unable to live independently prior cardiac arrest (required constant care; was unable to perform activities of daily living without the assistance of caregivers)? Yes □ / No □</td></tr>
</table>

PAGE 1/2

Figure 1. Questionnaire template — **A.** Page 1/2.

B

D	CPR attempted by EMS?: Yes ☐ / No ☐	Reason for CPR withdrawal *(if CPR attempted by EMS, please skip this question)*: obviously dead ☐ / DNAR ☐ / wish family ☐ / EMS decision ☐ / ROSC before EMS arrival ☐ / successful ICD-shock ☐
	(if CPR NOT attempted by EMS, please skip to part F)	
	First monitored rhythm after cardiac arrest: VF ☐ / pulseless VT ☐ / PEA ☐ / asystole ☐ / bradycardia ☐ / AED shockable *(if bystanders used AED before EMS arrival)* ☐ / AED nonshockable *(if bystanders used AED before EMS arrival)* ☐	
	Defibrillation: Yes ☐ / No ☐	*If YES:* Number of shocks ☐☐ Time of the first shock *(hh:mm)* ☐☐:☐☐
	Airway control during CPR: oropharyngeal tube ☐ / nasopharyngeal tube ☐ / laryngeal mask/tube ☐ / endotracheal tube ☐ / surgical airway ☐ / none used ☐ / other ☐ *(which?)*……	
	Ventilation during CPR: bag valve mask ☐ / respirator ☐	
	Drugs given during CPR: Adrenaline ☐ / Atropine ☐ / Amiodarone ☐ / Lidocaine ☐ / Heparin ☐ / Alteplase ☐ / Fluid therapy ☐ / Glucose solution ☐ / Magnesium sulfate ☐ / Calcium chloride ☐ / Sodium bicarbonate ☐ / Other ☐ *(which?)*……	
	Vascular access: IV ☐ / IO ☐ / endotracheal ☐	
	Mechanical CPR: Yes ☐ / No ☐	
E	Did the patient achieve ROSC at any point during CPR? Yes ☐ / No ☐ *(if NO, please skip to part F)*	
	Results of measurements after ROSC: BP ☐☐☐/☐☐☐ mmHg; glycemia ☐☐☐ mg/dl;	
	GCS after ROSC: ☐☐ points	
	Procedures after ROSC: 12-Lead ECG ☐ ; ECG transmission ☐ ; cardioversion ☐ ; transthoracic pacing ☐; targeted temperature management ☐	
	ECG description……	
	Presence of STEMI *(in 12-Lead ECG performed after ROSC)*: Yes ☐ / No ☐	
F	Patient's status *(check the appropriate box)*:	
	Transfer to the hospital with sustained ROSC ☐ → *or*	Time of hospital admission *(hh:mm)*: ☐☐:☐☐ Hospital name: Address of the hospital:
	Transfer to the hospital with ongoing CPR ☐ → *or*	
	Withholding CPR ☐ →	Time of the decision to withhold CPR *(hh:mm)*: ☐☐:☐☐

Thank you for completing our survey!

PAGE 2/2

Figure 1. cont. Questionnaire template — **B.** Page 2/2.

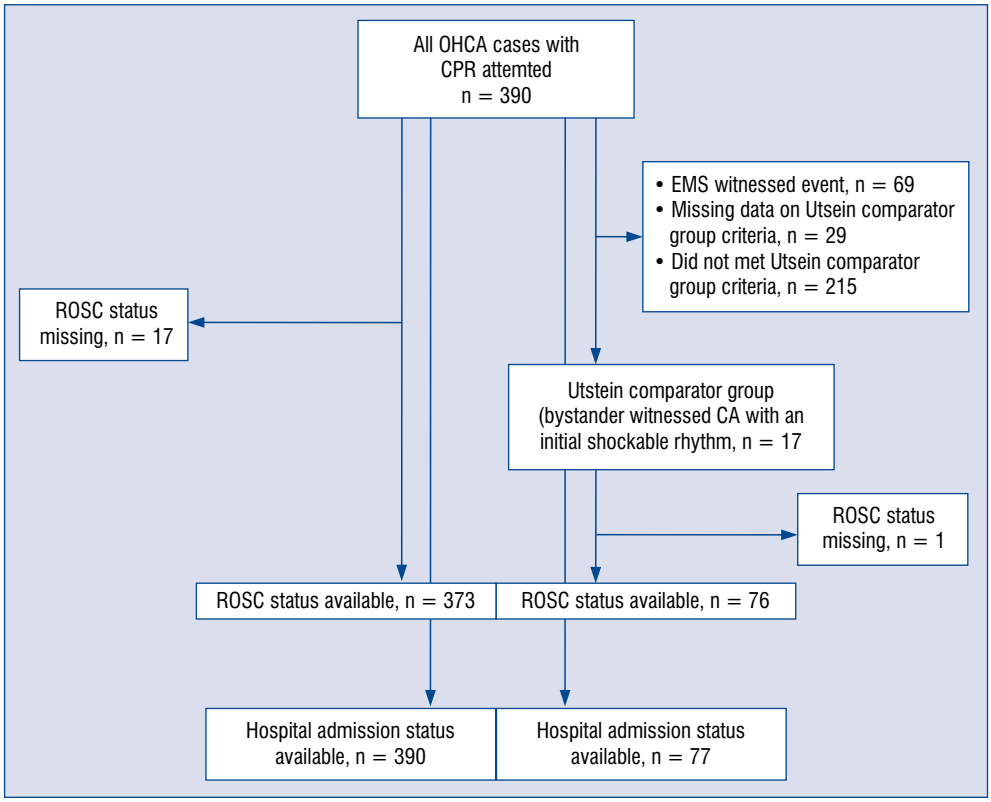

Figure 2. Flow-chart of the pilot study population; CA — cardiac arrest; CPR — cardiopulmonary resuscitation; EMS — emergency medical services; OHCA — out-of-hospital cardiac arrest; ROSC — return of spontaneous circulation.

by the EMS, that transferred the patient to the hospital or decided to stop CPR are taken into consideration. Subsequently, all questionnaires are transferred to the headquarters of Voivodeship Rescue Service, where they are archived digitally.

The questionnaire template, as well as all terms and definitions used in SIL-OHCA are based on the updated Utstein guidelines on reporting OHCA (2015) [1].

Follow-up

All patients transferred to the hospital by EMS are followed-up for a minimum of 1 year from the OHCA occurrence for all-cause mortality during initial hospitalization, within 30 days and at 12 months. The follow-up data will be sourced from the SILesian CARDiovascular (SILCARD) database, which is a joint initiative of the Silesian Center for Heart Diseases and the National Health Fund. SILCARD is a registry of administrative data, which comprises inter alia patients hospitalized due to OHCA within the Silesian Voivodeship area. Detailed information on the SILCARD registry have been published previously [12]. Data from the SILCARD registry enables to determine the etiology of OHCA (based on the final diagnosis during the first hospitalization after OHCA) to assess the percentage of patients who underwent procedures such as myocardial revascularization or cardioverter-defibrillator implantation, and to estimate the percentage of patients undergoing cardiac and neurological rehabilitation. Prehospital and follow-up data will be linked based on a patient's date of birth, individual code of the unit (hospital, department) to which the patient was transferred and the date of admission to the unit. An estimated percentage of patients who survived beyond admission to hospital, and for whom follow-up was available in more than 99% of patients with available date of birth and admission status. The percentage of patients with accessible date of birth in the pilot study was 96.1% and admission status was available for all patients. In cases where data linking baseline characteristics with follow-up are ambiguous i.e. more than 1 patient born on the same day is admitted to a given unit on a given day then patient follow-up data will not be taken into consideration. Based on currently available SILCARD data, it was estimated that the percentage of these patients would not exceed 1%.

The study conformed to the Declaration of Helsinki. Approval for research was waived by the

Bioethics Committee of the Silesian Medical Chamber, given the observational nature of the study.

Statistical analysis

Dichotomous variables are presented as number of cases (percentage). Continuous variables are presented as median and (interquartile range [IQR]). Analysis of the pilot-study data was performed both for the whole cohort of EMS-treated patients, as well as the subgroup of patients with bystander witnessed cardiac arrest and an initial shockable rhythm (Utstein comparator group [1]). There were no prespecified analyses in the SIL-OHCA registry.

Results

Results of 3-month pilot study

During the 3-month pilot phase of the study there were 390 cases of OHCA (128 women, 262 men), which is 0.6% of EMS responses during the period analyzed. A flow-chart of the pilot study population is presented in Figure 2. The median age of patients was 66 years (range 0–97 years; IQR 56–77 years). It was estimated that there are about 1560 cases of OHCA in the area covered per year, which corresponds with the 57 cases per 100,000 population per year. Baseline characteristics of the study population is shown in Table 2. The most frequent etiology of OHCA was medical. Asystole was the most common initial rhythm. Shockable rhythm was present in 25.8% of patients. The most frequent location of OHCA was home/residence, and 89.9% of events were witnessed. CPR was performed by bystander witnesses in 47.9% of OHCA cases. Automated external defibrillator (AED) was used by witnesses in 3 (0.8%) patients. ROSC occurred in 35.1% of the whole cohort, and in 51.3% of patients who met the Utstein comparator group criteria (bystander witnessed cardiac arrest with an initial shockable rhythm). In the whole study group, 28.7% of patients were admitted to hospital, including 2.8% of patients who were admitted during ongoing CPR. In the Utstein comparator group, 41.6% of patients were admitted to hospital, including 1.5% of patients during ongoing CPR.

Discussion

Large-scale medical registries are the primary source of information on the epidemiology of OHCA [2, 13, 14]. They enable analyzing trends in the occurrence, treatment approaches and prognosis in OHCA [15, 16]. International EuReCa One study encompassing 10,682 OHCA cases in 27 European countries have indicated substantial differences in the frequency of OHCA and survival to hospital discharge among participating countries [2]. In this registry 275 patients with OHCA from Poland were included, and inhabited only small cities (< 100,000 inhabitants) or villages [2]. The biggest prospective registry of OHCA in the Polish population was described by Cebula et al. [8], who provided a lot of valuable information on epidemiology of OHCA, however it did not include long-term follow-up. Aforementioned limitations of the previous studies provided reasons to introduce SIL-OHCA covering a population of 2.7 million inhabitants, residing in the highly urbanized region of Upper Silesia.

To the best of our knowledge, there have been published results in one prospective and three retrospective registries encompassing the Polish population to date [8, 17–19], as well as data from Poland which was reported in the international EuReCa ONE study [2]. The frequency of OHCA with attempted CPR was 70–128 cases per 100,000 population per year in these registries. The incidence of OHCA in the Upper Silesian population was estimated on the basis of the present 3-month pilot study when there were 57 cases per 100,000 inhabitants per year, which was close to the mean frequency in the European population (49 cases/100,000 inhabitants per year) [2]. Approximately two-thirds of patients with OHCA included in the examined registry were male, this finding was similar to other studies [8, 18]. ROSC in the present population was achieved in 35.1% of patients, which confirms previously published data from Poland, where ROSC occurred in 30.5–31.2% of cases [8, 18]. In addition, in a homogeneous sub-population meeting Utstein comparator group criteria, the ROSC frequency was 51.3%, which corresponds to data from European registries and is slightly lower than that reported on average in Europe (56.8%) [2]. Finally, of all patients with OHCA included in the pilot study, 25.9% survived the event (were transferred to the hospital with sustained ROSC). This finding is also very similar to the results of EuReCa ONE, where the event survival rate was 25.2% [2].

The results of the present 3-month pilot study have indicated an inadequate participation of bystanders in CPR before the arrival of EMS, which has a significant impact on the percentage of cases with shockable rhythm, and long-term outcome [20–22]. Hasselqvist-Ax et al. [20] reported, based on data from nationwide Swedish registry of OHCA,

Table 2. Demographic data, baseline characteristics and outcome of patients with OHCA included in Silesian Registry of Out-of-Hospital Cardiac Arrest.

Variable	Whole population (n = 390)	Percentage of cases with missing data
Age [years]	66 [56–77]	3.8
Sex:		0
Male	262 (67.2)	
Female	128 (32.8)	
OHCA etiology:		1.5
Medical	299 (77.9)	
Asphyxial	44 (11.5)	
Traumatic	9 (2.3)	
Other	32 (8.3)	
Location of OHCA:		0.2
Home/residence	282 (72.5)	
Public space	64 (16.5)	
Other	43 (11.1)	
Response time [min]	8 [6-11]	1.3
EMS witnessed OHCA	69 (17.9)	0
Bystander CPR	186 (47.9)	0.5
Comorbidities:		0
Previous MI	51 (13.1)	
Previous stroke	37 (9.5)	
Malignancies	27 (6.9)	
Previously implanted cardioverter-defibrillator	4 (1.0)	0
First monitored rhythm:		4.6
VF/pulseless VT	96 (25.8)	
Asystole/PEA	276 (74.2)	
12-lead ECG performed after ROSC	54 (41.2)	0
Presence of STEMI	16 (29.6)	58.8
Patients who met the Utstein comparator group criteria (bystander witnessed CA with an initial shockable rhythm)	77 (19.7)	7.4
ROSC (whole population)	131 (35.1)	4.4
Status of patients on hospital admission (whole population):		0
Died before hospital admission	278 (71.3)	
Admission to hospital with ROSC	101 (25.9)	
Admission to hospital during ongoing CPR	11 (2.8)	
ROSC (Utstein comparator group)	39 (51.3)	1.3
Status of patients on hospital admission (Utstein comparator group):		0
Died before hospital admission	45 (58.4)	
Admission to hospital with ROSC	31 (40.3)	
Admission to hospital during ongoing CPR	1 (1.3)	

Dichotomous variables are presented as number of cases (percentage). Continous variables are presented as median (intequartile range); CA — cardiac arrest; CPR — cardiopulmonary resuscitation; ECG — electrocardiography; OHCA — out-of-hospital cardiac arrest; MI — myocardial infarction; PEA — pulseless electrical activity; ROSC — return of spontaneous circulation; STEMI — ST-elevation myocardial infarction; VF — ventricular fibrillation; VT — ventricular tachycardia

that CPR performed by bystanders was associated with 30-day survival, which is more than twice as high as that associated with no CPR before EMS arrival. A high percentage of cases with CPR performed before EMS arrival in Sweden is probably due to the fact that almost one third of the Swedish population have undergone CPR training during the past three decades [20, 23]. In this context Sweden is a role model for other nations [23]. In addition, Nakahara et al. [21] reported that in Japan, between 2005 and 2012, increase in neurologically intact survival in patients with OHCA was observed, which was associated with an increased rate of bystander CPR. Another critical element of the "chain of survival", besides CPR, is rapid defibrillation [24]. Hansen et al. [25] showed that over 30% of patients with OHCA, who were defibrillated by bystanders, survived to hospital discharge. The AED was used by bystanders in less than 1% of cases included in SIL-OHCA, which may have been be due to the low availability of AED, as well as insufficient knowledge of society about the possibility of using the device. The use of AED by bystanders in the present population was over five times lower than reported in the United States, according to study by van Diepen et al. [26]. Aforementioned factors affect an unsatisfactory percentage of ROSC, as well as the percentage of patients admitted to the hospital with sustained ROSC, which, despite being close to the outcomes reported on average in the European population, is lower than results achieved in some Western European countries [2, 27, 28]. There is a critical need for interventions to increase the frequency of bystander CPR and AED use in the Polish population to improve survival rate in patients with OHCA.

The SIL-OHCA registry, which is an initiative of the Voivodeship Rescue Service in Katowice in cooperation with the Silesian Center for Heart Diseases in Zabrze, is, to the best of our knowledge, the first prospective OHCA registry which aims to assess long-term prognosis for this group of patients in Poland. Results of the 3-month pilot study confirmed the possibility of creating registry which covers all patients with OHCA in the region of activity of Voivodeship Rescue Service in Katowice. In the pilot phase of the study, the percentage of missing data was low, and results presented were comparable to previous studies. We believe that the SIL-OHCA registry will provide reliable epidemiological data on OHCA, including the prehospital data and long-term follow-up. Owing to the data collected, it will be possible to identify factors that need improvement in order to increase both the short- and long-term survival rates of patients with OHCA.

Conclusions

Short-term results of OHCA patients in Poland are still unsatisfactory. It is believed that owing to the prospective registry, medical practitioners will be able to identify factors that require modification in order to improve short- and long-term prognosis in patients with OHCA.

Conflict of interest: None declared

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VIA MEDICA

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Influence of QRS duration and axis on response to cardiac resynchronization therapy in chronic heart failure with reduced left ventricular ejection fraction: A single center study including patients with left bundle branch block

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Abstract

Background: *The aim of the study was to evaluate QRS duration and axis as predictors of response to cardiac resynchronization therapy (CRT) in order to reduce the proportion of non-responders.*

Methods: *Retrospective single-center study including 42 CRT recipients, with left bundle branch block (LBBB), left ventricular ejection fraction (LVEF) < 40%, in New York Heart Association (NYHA) class ≥ II. Response to CRT was declared as NYHA class improvement ≥ 1 (symptomatic) and LVEF improvement by ≥ 10% (echocardiographic) > 6 months post implantation.*

Results: *Symptomatic responders had longer pre- (172.3 ± 17.9 vs. 159.0 ± 18.3 ms; p = 0.027) and postimplantation (157.2 ± 24.1 vs. 136.7 ± 23.2 ms; p = 0.009) QRS duration. Preimplantation QRS < 150 ms predicted poor response (odds ratio [OR] for response vs. lack of response 0.04; 95% confidence interval [CI] 0.001–0.74). Predictors of symptomatic response included: postimplantation QRS > 160 ms (OR 7.2; 95% CI 1.24–41.94), longer QRS duration before (OR for a 1 ms increase 1.04, 95% CI 1.00–1.08) and post implantation (OR for a 1 ms increase 1.04; 95% CI 1.01–1.07). Area under the curve (AUC) for pre- and postimplantation QRS duration was 0.672 (95% CI 0.51–0.84) and 0.727 (95% CI 0.57–0.89), respectively, with cut-off points of 178.5 ms and 157 ms. For post implantation QRS axis, AUC was 0.689 (95% CI 0.53–0.85), with cut-off points of –60.5° or –38.5°. Preimplantation QRS axis was the only predictor of echocardiographic response (OR 0.98; 95% CI 0.96–1.00), with AUC of 0.693 (95% CI 0.54–0.85) and a threshold of –36°.*

Conclusions: *Marked pre- and postimplantation QRS prolongation and preimplantation negative QRS axis deviation are moderate predictors of response to CRT.* (Cardiol J 2020; 27, 5: 575–582)

Key words: cardiac resynchronization therapy, heart failure, left bundle branch block, QRS axis

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Introduction

Cardiac resynchronization therapy (CRT) is a well-proven beneficial treatment strategy for patients with chronic heart failure and reduced left ventricular ejection fraction (HF-rEF), and prolonged QRS duration [1]. Large studies have demonstrated that this therapeutic option not only reduces mortality and morbidity, but also improves symptoms and quality of life [2–4]. However, a significant proportion of patients treated with CRT do not achieve the desired response, emphasizing the need for better selection criteria [5]. Previous studies have recognized some simple electrocardiographic parameters, such as QRS morphology, duration and axis, as predictors of response to CRT [6–8]. However, the data are still sparse and inconclusive, particularly with regard to the predictive role of QRS axis in CRT candidates, and no threshold values for QRS axis have been established so far regarding positive response to CRT.

Thus, the aim of this study was to evaluate the potential usefulness of QRS duration and QRS axis orientation in predicting symptomatic (SR) and echocardiographic response (ER) to CRT in HF-rEF patients with left bundle branch block (LBBB).

Methods

Study design and patients

The study is a retrospective single-arm, single-center analysis including Caucasian patients implanted with cardiac resynchronization therapy-defibrillators (CRT-D) at the Department of Cardiology and Internal Medicine, Dr. A. Jurasz University Hospital No. 1 in Bydgoszcz from July 2010 through April 2016. All study participants were adults (> 18 years of age) with QRS duration > 120 ms, LBBB QRS morphology, left ventricular ejection fraction (LVEF) < 40%, and functional capacity of at least class II according to the New York Heart Association (NYHA) functional classification. Various transvenous delivery systems, left ventricle (LV) leads, and CRT-D devices from different companies were used. The most frequent target for LV lead placement was the posterolateral aspect of the LV. Apical positions were avoided. All LV leads were implanted intravenously. The VV interval was set between –20 and 0 ms, and the atrio-ventricular (AV) interval between 100–120 ms for sensed and 140–160 ms for paced atrial events. Presence of anodal LV pacing was excluded through programming LV pacing to bipolar or by confirmation of the presence of biventricular pacing morphology on electrocardiogram (ECG) in case of other configurations of LV pacing. No echocardiographic optimization of the device settings after implantation was implemented. LVEF was calculated by experienced echocardiographers using the modified Simpson rule. Pharmacotherapy in study participants was in line with the recommendations of the European Society of Cardiology. Patients undergoing an upgrade of conventional devices to CRT or a CRT replacement and those with incomplete data regarding electrocardiographic or echocardiographic parameters were excluded. All data were extracted from discharge cards, echocardiography and electrocardiography examinations. The study protocol was approved by the Bioethics Committee of the Nicolaus Copernicus University in Torun (Poland).

Electrocardiograms

A standard 12-lead ECG was recorded at a speed of 25 mm/s during the index hospitalization before and after the implantation procedure. Visual assessment of ECG recordings was performed by two independent researchers. The QRS duration was measured with a manual caliper in all 12 leads and the highest result was considered for further analysis. The preimplantation QRS duration was divided into three groups: < 150, 150–199, and ≥ 200 ms [6]. Similarly, postimplantation QRS duration was classified into three groups (< 120, 120–160, and > 160 ms) [6]. QRS axis was measured in leads I, II and aVF according to the method described in the literature [9]. QRS axis both as a quantitative value (expressed in degrees) and a qualitative category are presented. Normal axis was defined for values ranging between +90° and –30°, right axis deviation (RAD) for values between +90° and 180°, left axis deviation (LAD) for values between –30° and –90° and extreme axis deviation (EAD) for values between –90° and 180°. LBBB was diagnosed according to Polish Cardiac Society recommendations as: QRS duration ≥ 120 ms, with broad, slurred R-wave or R-wave with plateau at its peak in leads I, aVL, V5, and V6, with QS or rS morphology in leads V1–V3, intrinsicoid deflection in leads V5, V6 of > 60 ms, and secondary ST-T changes opposite to the major QRS direction [10].

Response to CRT

Response to CRT was independently evaluated using two parameters: NYHA class for SR and LVEF for ER. SR was defined as improvement in NYHA classification by ≥ 1 class [6, 8]. Improvement in absolute LVEF ≥ 10% was defined as ER.

The clinical and echocardiographic follow-up was performed at least 6 months after implantation.

Statistical analysis

The statistical analysis was performed with IBM SPSS Statistics version 23. P values < 0.05 were considered statistically significant. Normality of data distribution was tested with the Shapiro-Wilk test. Continuous variables were presented as mean ± standard deviation. Absolute frequency and percentages were reported for categorical data. The differences between paired variables were calculated with the appropriate Student t-test or Wilcoxon Signed Rank test according to normality of data distribution. Similarly, the differences between non-paired variables were calculated with the appropriate Student t-test or Mann-Whitney test according to normality. The χ^2 test was performed for all categorical data. Odds ratios (OR) were reported with 95% confidence intervals (CI). The parameters tested as potential predictors of response to CRT included: QRS duration, QRS duration reduction, QRS axis and QRS axis change. All parameters were analyzed for SR and ER. Receiver operator characteristic (ROC) curves with particular cut-off points, specificity, and sensitivity were calculated for parameters with significant impact on the response.

Results

Patients

Among all patients who received CRT-D within the study period, 42 met the inclusion criteria. The average age at implantation was 66.4 ± 8.3 years, with predominance of men (54%). The mean follow-up time was 29 ± 18.6 months. Baseline data for all patients including clinical parameters, preimplantation ECG and echocardiographic measurements are shown in Table 1.

Mean QRS duration at baseline exceeded 160 ms. The majority of patients (73.8%) presented native QRS duration between 150 and 199 ms. Wider QRS complexes (≥ 200 ms) were found in 9.5% of cases, while 16.7% of patients had QRS duration shorter than 150 ms, but not shorter than 130 ms. After the implantation a reduction in mean QRS duration by 19.5 ± 23.0 ms was observed. In 21.4% of patients QRS duration increased or remained unchanged.

Patients with normal QRS axis and LAD accounted for 95.3% of the study population. Detailed data on the distribution of QRS axis are presented in Table 1. Pre- and postimplantation mean QRS axis was –26.4 ± 41.7° and –47.9 ± 89.2°, respectively, corresponding to a mean change of –21.5 ± ± 97.2°. The direction of the change was towards more negative values in 69% of patients and towards more positive values in the remaining 31% of cases.

Table 1. Patient baseline characteristics (n = 42).

Variable	Value
Age [years]	66.4 ± 8.3
Sex:	
Female	19 (45.2%)
Male	23 (54.8%)
Etiology:	
Ischemic cardiomyopathy	31 (73.8%)
Non-ischemic cardiomyopathy	11 (26.2%)
Hypertension	28 (66.7%)
Diabetes mellitus	18 (42.9%)
Hyperlipidemia	10 (23.8%)
Obesity	8 (19.0%)
NYHA class:	
II	13 (31.0%)
II/III	15 (35.7%)
III	12 (28.6%)
IV	1 (2.4%%)
LVEF [%]	26.7 ± 5.5
QRS duration [ms]	164.0 ± 19.1
QRS axis:	
Normal	22 (52.4%)
LAD	18 (42.9%)
RAD	1 (2.4%)
EAD	1 (2.4%)
QRS axis [°]	–26.4 ± 41.7

Data are presented as numbers and percentages or means ± standard deviations. EAD — extreme axis deviation; LAD — left axis deviation; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association; RAD — right axis deviation

At follow-up a reduction in mean NYHA class (2.55 ± 0.48 vs. 2.02 ± 0.44; $p < 0.001$), improvement in LVEF (26.7 ± 5.5 vs. 34.2 ± 10.3%; $p < 0.001$) and a reduction in QRS duration (164.0 ± 19.1 vs. 144.5 ± 25.4 ms; $p < 0.001$) were found. The numeric change in QRS axis was statistically insignificant (–26.4 ± 41.7 vs. –47.9 ± 89.2°; $p = 0.11$).

Symptomatic response

Symptomatic response was achieved in 16 (38%) patients. The responders, in comparison with non-responders, had a significantly higher baseline NYHA class, lower NYHA class at follow-up and

wider QRS complex before and after implantation (Table 2). The analysis of potential predictors of response to CRT revealed that patients with QRS < 150 ms before the procedure were less likely to respond well to CRT, while patients with QRS > 160 ms after the procedure had a greater chance to become responders to CRT (OR 7.2; 95% CI 1.24–41.94). Longer QRS duration was associated with a better response, when measured before as well as after implantation of the device. ROC curves calculated for parameters found to be predictors of SR are presented in Figure 1. Area under the curve (AUC) for QRS duration before the procedure was 0.672 (95% CI 0.51–0.84; p = 0.037) with an optimal cut-off point of 178.5 ms (sensitivity 31.3%, specificity 84.6%). AUC calculated for postimplantation QRS duration was 0.727 (95% CI 0.57–0.89; p = 0.005) with an optimal cut-off point of 157 ms (sensitivity 56.3%, specificity 73.1%). For postimplantation QRS axis, the AUC was 0.689 (95% CI 0.53–0.85; p = 0.025), with a cut-off point of –60.5° yielding sensitivity of 62.5% and specificity of 61.5%. Shifting the cut-off point to –38.5° resulted in a sensitivity drop down to 50%, with a concomitant increase in specificity up to 76.9%.

Echocardiographic response

Echocardiographic response was found in 19 (45%) patients. The responders, in comparison with non-responders, had significantly lower LVEF values at baseline and substantially higher LVEF at follow-up (Table 3). The QRS axis before the procedure was significantly more negative among responders as compared with non-responders. Postimplantation QRS axis trended to be more negative among responders. More negative QRS axis before CRT was associated with a better ER in univariate analysis (Table 3). ROC curve was calculated for QRS axis before the procedure and AUC for this parameter was 0.693 (95% CI 0.54–0.85; p = 0.018) with an optimal cut-off point of –36° (sensitivity 63.2%, specificity 69.6%).

Discussion

Cardiac resynchronization therapy remains the cornerstone of treatment for drug-refractory HF-rEF patients and wide QRS complex, particularly those with LBBB. This single-center study aimed to assess the role of pre- and postimplantation ECG for prediction of long-term response to CRT in patients with HF-rEF and LBBB. The main finding of this study is that simple electrocardiographic patterns can predict the SR and ER to this therapy. However, the predictive value of electrocardiographic parameters in this setting seems to be moderate. In detail, the present research indicates that: 1) SR is determined by QRS duration, 2) preimplantation QRS duration of more than 150 ms, but less than 178.5 ms predicts SR, 3) ER is determined by the QRS axis, 4) this relation is insignificant for qualitative estimates of the QRS axis, however in quantitative assessment preimplantation QRS axis of less than –36° predicts ER.

The true target for CRT is the mechanical dyssynchrony of the LV and QRS duration is considered the primary sign of this condition. Prolonged QRS duration is related to disease severity and increased mortality in HF-rEF patients [11] and remains an important factor determining enrollment for various studies assessing CRT. Based on large clinical trials and retrospective analyses [12–15], the current European Society of Cardiology guidelines for CRT restricted the highest class of recommendations to patients with QRS duration of > 150 ms are considered to achieve the most favorable response [1]. However, even though QRS duration was recognized as an important indicator of CRT effectiveness, a significant percentage of patients receiving this treatment still fail to benefit despite widened QRS [5]. A more precise analysis of prolonged QRS duration as a response predictor is required, however the data is limited. Kronborg et al. [6] reported an increased rate of SR to CRT in patients with QRS duration between 150 and 200 ms, compared with those with a shorter (< 150 ms) or longer QRS duration (> 200 ms). Sassone et al. [7] demonstrated that responsiveness to CRT in patients with LBBB decreases starting from QRS duration of around 180 ms onward. In the present study, the upper cut-off value of QRS duration to predict non-responsiveness was 178.5 ms. These similar results confirm that there is a limit of mechanical dyssynchrony of LV, visually represented in ECG, above which CRT fails to provide significant benefit.

In contrast to literature data showing that the extent of QRS duration reduction after CRT implantation is a marker of subsequent response to CRT (the higher the reduction, the better the response), this study demonstrated a higher likelihood of response to CRT in patients with QRS duration > 160 ms on biventricular pacing (OR 7.2, 95% CI 1.24–41.94). This unexpected finding perhaps might be explained by the fact that one of the response classifiers to be used in the present study was the NYHA classification — a method well

Table 2. Symptomatic response to CRT (NYHA class improvement ≥ 1): comparison of responders and non-responders, and electrocardiographic predictors of response to CRT in univariate analysis.

Variable	Non-responders (n = 26)	Responders (n = 16)	P
NYHA class at baseline	2.3 ± 0.31	2.9 ± 0.5	< 0.001
NYHA class at follow-up	2.2 ± 0.3	1.8 ± 0.5	0.006
LVEF preimplantation [%]	26.3 ± 5.5	27.5 ± 5.7	0.49
LVEF postimplantation [%]	32.7 ± 9.7	36.7 ± 11.0	0.22
QRS duration (preimplantation) [ms]	159.0 ± 18.3	172.3 ± 17.9	0.027
QRS duration (postimplantation) [ms]	136.7 ± 23.2	157.2 ± 24.1	0.009
QRS duration change [ms] (difference between post-implantation and preimplantation QRS duration)	–22.2 ± 21.2	–15.1 ± 25.8	0.33
QRS axis (preimplantation) [°]	–28.4 ± 43.4	–23.2 ± 40.0	0.7
QRS axis (post-implantation) [°]	–71.3 ± 76.8	–9.9 ± 97.0	0.028
QRS axis change [°] (difference between postimplantation and preimplantation QRS axis)	–42.9 ± 93.8	13.3 ± 95.3	0.068
Variable	**OR**	**95% CI**	**P**
Electrocardiographic predictors of response to CRT			
QRS duration (preimplantation)* [ms]			
< 150	0.04	0.001–0.74	0.033
150–199	3.69	0.82–16.65	0.49
≥ 200	5.77	0.54–61.13	0.15
QRS duration (postimplantation)* [ms]			
< 120	0.28	0.03–2.65	0.38
120–160	0.47	0.13–1.75	0.32
> 160	7.2	1.24–41.94	0.038
QRS duration (preimplantation) for a 1 ms increase	1.04	1.00–1.08	0.04
QRS duration (postimplantation) for a 1 ms increase	1.04	1.01–1.07	0.02
QRS axis (preimplantation)			
Normal	0.86	0.25–2.99	0.99
LAD	1.06	0.30–3.73	0.99
QRS axis (postimplantation)*			
Normal	0.69	0.13–3.74	0.99
LAD	1.23	0.31–4.83	0.99
RAD	4.0	0.64–25.02	0.18
EAD	0.33	0.08–1.30	0.2
QRS axis (preimplantation) for a 1° increase	1.00	0.99–1.02	0.69
QRS axis (postimplantation) for a 1° increase	1.01	1.00–1.02	0.04
No QRS axis change	1.91	0.45–8.05	0.47
QRS duration reduction	0.71	0.16–3.16	0.71
QRS axis decrease	0.39	0.10–1.50	0.19

*Asterisk signifies that each category of the parameter was compared against all remaining categories joined together. CI — confidence interval; CRT — cardiac resynchronization therapy; EAD — extreme axis deviation; LAD — left axis deviation; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association Class; OR — odds ratio; RAD — right axis deviation

known for its subjectivity. Moreover, the majority of our patients (66.7%) presented with mild heart failure (NYHA class II), which is probably why the beneficial effect of CRT could be noticed primarily in patients with a high degree of underlying cardiac pathology and ventricular dyssynchrony as evidenced by largely widened QRS complexes, even on biventricular pacing. Unexpectedly, it was noted

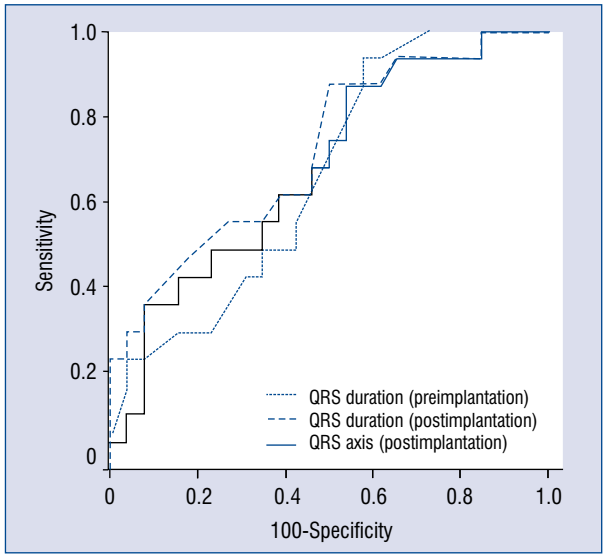

Figure 1. Receiver operator characteristic curves for predictors of symptomatic response to cardiac resynchronization therapy: preimplantation QRS duration (AUC 0.672 [95% CI 0.51–0.84]; p = 0.037), postimplantation QRS duration (AUC 0.727 [95% CI 0.57–0.89]; p = 0.005) and postimplantation QRS axis (AUC 0.689 [95% CI 0.53–0.85]; p = 0.025).

that there was no statistical difference in pre- and post implantation QRS duration in echocardiographic responders vs non-responders, however for symptomatic response assessment non-responders had significantly wider QRS duration, as expected. Possible explanations for this discrepancy might include a low number of participants enrolled in the study as well as a high percentage of patients with ischemic cardiomyopathy, with the latter being a risk factor of poorer resynchronization and response to CRT.

Previous studies provide consistent evidence of the importance of QRS duration in predicting response to CRT [2, 3, 6, 7, 12, 14, 15]. However, according to available research, only a few studies aimed to highlight the value of preimplantation QRS axis as a possible predictor of therapy success in LBBB patients, providing inconsistent results. In a study including 78 patients with LBBB receiving CRT, Garcia-Seara et al. [8] found that patients with LAD demonstrated a more favorable response (improvement in functional class, increase in LVEF of 5%, no hospital admissions for HF and remained alive throughout follow-up) than those with normal QRS axis. Also, Kronborg et al. [6] reported increased mortality and a lower likelihood of ER (improvement in absolute LVEF by 5%) in patients with RAD compared with normal axis or LAD. On the contrary, according to Brenyo et al. [16] the presence of LAD in LBBB is associated with less benefit from CRT. Similarly, Perotta et al. [17] suggest that the presence of LAD or RAD is associated with a significant risk of worse response.

In the present study, no significant differences were seen in response to CRT with respect to the qualitative categorization of the QRS axis. However, this study takes an important subsequent step in examining the efficacy of CRT in the LBBB population, relying on the quantitative value of QRS axis deviation. It was found that in a community-based cohort a more negative value of preimplantation QRS axis with a cut-off point of –36° was associated with a higher rate of response to CRT. Importantly, established herein was a successful cut-off point that distinguishes the predictive value of the QRS axis. It is believed that this finding is of particular interest, however further randomized controlled studies examining these conclusions with a greater number of patients in different environments are necessary.

Limitations of the study

The present study presents typical limitations of a retrospective single-center analysis. Therefore, the findings warrant confirmation in further larger prospective studies. Additionally, the investigated group was heterogeneous and there were different clinical and echocardiographic observers during the study period. It was not possible to define a specific point in time for the follow-up due to retrospective character of the study and lack of routinely scheduled long-term echocardiography examinations in patients treated with CRT. Thus, only patients with echocardiographic examination performed at least 6 months after the device implantation were included as this is the minimum period to observe changes in ejection fraction due to LV remodeling. Another major limitation is the small study group, which potentially exposed the results to type II error. Furthermore, due to a limited sample size the present study did not evaluate other causes for the lack of response to CRT, not associated with pacing, and multivariate analysis was not performed. There was also an inability to perform sub-analyses of the main study results. Only 2 patients in this study had axis other than normal or left deviated (one had RAD and one had EAD). However, the proportion of RAD patients in the present group (2.4%) is comparable to data presented in the literature (e.g. Kronborg et al. [6] reported 4% patients with RAD and LBBB). Finally, lower rates of responders to CRT were

Table 3. Echocardiographic response to CRT (absolute LVEF increased by ≥ 10%): comparison of responders and non-responders, and electrocardiographic predictors of response to CRT in univariate analysis.

	Non-responders (n = 23)	Responders (n = 19)	P
NYHA class at baseline	2.54 ± 0.54	2.55 ± 0.4	0.7
NYHA class at follow-up	2.02 ± 0.53	2.03 ± 0.31	0.94
LVEF preimplantation [%]	28.5 ± 5.0	24.6 ± 5.5	0.02
LVEF postimplantation [%]	27.8 ± 6.0	42.1 ± 8.8	< 0.001
QRS duration (preimplantation) [ms]	161.0 ± 20.3	167.6 ± 17.3	0.27
QRS duration (postimplantation) [ms]	142.8 ± 25.1	146.6 ± 26.2	0.63
QRS duration change [ms] (difference between postimplantation and preimplantation QRS duration)	–18.3 ± 25.4	–21.0 ± 20.4	0.71
QRS axis (preimplantation) [°]	–13.1 ± 34.7	–42.6 ± 44.6	0.021
QRS axis (postimplantation) [°]	–27.0 ± 98.1	–73.3 ± 71.4	0.09
QRS axis change [°] (difference between postimplantation and preimplantation QRS axis)	–13.9 ± 105.4	–30.7 ± 88.3	0.58
Variable	**OR**	**95% CI**	**P**
Electrocardiographic predictors of response to CRT			
QRS duration (preimplantation)* [ms]			
< 150	0.42	0.07–2.46	0.43
150–199	1.64	0.40–6.76	0.73
≥ 200	1.24	0.16–9.75	0.99
QRS duration (postimplantation)* [ms]			
< 120	0.56	0.09–3.45	0.67
120–160	0.75	0.21–2.72	0.75
> 160	2.38	0.49–11.62	0.43
QRS duration (preimplantation) for a 1 ms increase	1.019	0.99–1.05	0.27
QRS duration (postimplantation) for a 1 ms increase	1.01	0.98–1.03	0.62
QRS axis (preimplantation)			
Normal	0.31	0.09–1.10	0.12
LAD	2.08	0.60–7.22	0.35
QRS axis (postimplantation)*			
Normal	0.89	0.17–4.58	0.99
LAD	1.31	0.34–5.01	0.74
RAD	0.20	0.02–1.89	0.2
EAD	1.69	0.49–5.86	0.53
QRS axis (preimplantation) for a 1° increase	0.98	0.96–1.00	0.03
QRS axis (postimplantation) for a 1° increase	0.997	0.99–1.004	0.40
No axis change	1.29	0.31–5.35	0.99
QRS duration reduction	1.04	0.24–4.58	0.99
QRS axis decrease	1.49	0.39–5.66	0.74

*Asterisk signifies that each category of the parameter was compared against all remaining categories joined together. CI — confidence interval; CRT — cardiac resynchronization therapy; EAD — extreme axis deviation; LAD — left axis deviation; LVEF — left ventricular ejection fraction; NYHA — New York Heart Association Class; OR — odds ratio; RAD — right axis deviation; N — number of patients

reported when compared with other studies. This fact may have been caused by a high prevalence of established factors associated with poor response to CRT in the present study participants (i.e. ischemic etiology of HF-rEF, male patients and lower severity of symptoms).

Conclusions

The present study indicates that marked QRS prolongation in pre- and postimplantation assessment and preimplantation negative deviation of the QRS axis are moderate predictors of response to CRT in chronic heart failure patients with low LVEF and LBBB. In detail, substantial pre- and postimplantation QRS prolongation is associated with SR, while more negative pre-implantation QRS axis seems to predict echocardiographic response.

Conflict of interest: None declared

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Impact of routine invasive strategy on outcomes in patients with non-ST-segment elevation myocardial infarction during 2005–2014: A report from the Polish Registry of Acute Coronary Syndromes (PL-ACS)

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Abstract

Background: *Non-ST-segment elevation myocardial infarction (NSTEMI) has become the most frequently encountered type of myocardial infarction. The patient clinical profile and management has evolved over the past decade. As there is still a scarcity of data on the latest trends in NSTEMI, changes herein were observed and assessed in the treatment and outcomes in Poland between 2005 and 2014.*

Methods: *A total of 197,192 patients with NSTEMI who enrolled in the Polish Registry of Acute Coronary Syndromes (PL-ACS) between 2005 and 2014 were analyzed. In-hospital and 12-month mortality were assessed.*

Results: *Coronary angiography use increased from 35.8% in 2005–2007 to 90.7% in 2012–2014 ($p < 0.05$), whereas percutaneous coronary intervention increased from 25.7% in 2005–2007 to 63.6% in 2012–2014 ($p < 0.05$). There was a 50% reduction in in-hospital mortality (from 5.6% in 2005–2007 to 2.8% in 2012–2014; $p < 0.05$) and a 30% reduction in 1-year mortality (from 19.4% in 2005–2007 to 13.7% in 2012–2014; $p < 0.05$). A multivariate analysis confirmed an immense impact of invasive strategy on patient prognosis during in-hospital observation with an odds ratio (OR) of 0.31 (95% confidence interval [CI] 0.29–0.33; $p < 0.05$) as well as during the 12-month observation with an OR of 0.51 (95% CI 0.49–0.52; $p < 0.05$).*

Conclusions: *Over the past 10 years, an important advance in the management of NSTEMI has taken place in Poland. Routine invasive strategy resulted in a significant decrease in mortality rates in all groups of NSTEMI patients.* (Cardiol J 2020; 27, 5: 583–589)

Key words: non-ST-elevation myocardial infarction, invasive strategy, percutaneous coronary intervention, outcomes, temporal trends

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Introduction

Non-ST-segment elevation myocardial infarction (NSTEMI) represents the majority of all MI cases. In Western Europe, NSTEMI accounts for over 60% of all MI cases. Dynamic changes in the clinical profile and treatment strategy have been observed in recent years. Contemporary analyses for a wide national population are scarce.

The analysis of clinical characteristics, treatment strategies and outcomes in almost 200,000 NSTEMI cases registered in the Polish Registry of Acute Coronary Syndromes (PL-ACS) between 2005 and 2014 are presented.

Methods

The study population was drawn from 463 hospitals in Poland that provide care to patients with MIs. The population consists of patients admitted with a diagnosis of NSTEMI according to the European Society of Cardiology guidelines [1, 2]. The study covers a 10-year period from 2005 to 2014. Contribution to the study was voluntary; nevertheless, half of all estimated NSTEMI cases in Poland during the study time period were included. The study complies with the Declaration of Helsinki and was approved by the PL-ACS Registry committee.

Data were collected from PL-ACS Registry questionnaires that include variables on demographic factors (gender, age), risk factors (smoking, hypertension, hypercholesterolemia, diabetes mellitus and obesity), previous coronary incidences and related procedures (MI, percutaneous coronary intervention [PCI], coronary artery bypass grafting), clinical presentation on admission (Killip class, heart rate, systolic blood pressure), electrocardiographic abnormalities, left ventricular ejection fraction, coronary angiography (CA), coronary intervention details, and in-hospital and post-discharge treatment. The mortality rate was evaluated for the in-hospital observation period as well as for 30-day, 6-month and 12-month follow-up periods.

Statistical analysis

The gender groups were analyzed separately and subsequently compared to each other. To investigate the impact of age on outcomes, the analysis was conducted in age groups (< 55, 55–64, 65–74, ≥ 75 years) as well as in consecutive decades of life. Changes over time were investigated using the following two models: a comparison between subgroups in marginal 3-year intervals (2005–2007 and 2012–2014) and an evaluation of temporal trends over a 10-year period.

Categorical data are presented as numbers and percentages while continuous data are presented as the median or arithmetic mean ± standard deviation (SD). Differences in categorical variables were tested using the χ^2 test with Pearson modification, whereas in continuous variables differences were tested with the Student t-test. A two-sided p value ≤ 0.05 was considered significant. Trend importance was verified by the Cochran-Armitage test for categorical data and the Jonckheere-Terpstra test for continuous data. A logistic regression was used to identify variables that independently contributed to mortality.

Results

A total of 197,192 patients (including 77,550 women, 39.3%) hospitalized in Poland due to NSTEMI between 2005 and 2014 were included in the analysis. The contribution of younger patients (under 55) decreased compared to older patients. The average age of males increased from 65 to 66 while in women it was stable at 72. Nevertheless, men predominated in the group under 70, whereas women did in the group over 70.

The frequency of diabetes, arterial hypertension, obesity (in men only), and smoking (in women only) also increased. A history of prior coronary artery interventions (especially PCI) was more common in the later years were observed in this study (Table 1).

Over the last decade, NSTEMI treatment strategy has changed significantly. The frequency of coronary angiography increased from 35.8% in 2005–2007 up to 90.7% in 2012–2014; $p < 0.05$. From 2012 to 2014, the gender disparity in CA implementation was still visible with 88.4% in women vs. 92.1% in men; $p < 0.05$. PCI use increased from 25.7% in 2005–2007 to 63.6% in 2012–2014; $p < 0.05$. From 2012 to 2014 we achieved 59.6% in women and 66.1% in men; $p < 0.05$. The most intensive growth of an invasive procedure use took place between 2007 and 2011. In later years, only a mild further increase was observed. In 2014, only 10.9% of women and 7.1% of men ($p < 0.05$) were treated conservatively. Temporal trends in the invasive treatment of NSTEMI patients are presented in Figure 1.

The age group analysis revealed that the percentage of invasive treatment increased most in the oldest patients (over 75 years) and achieved a level of 80% in CA and 50% in PCI. Although differences

Table 1. Clinical characteristics of non-ST-elevation myocardial infarction patients.

Clinical characteristics	2005–2007			2012–2014			2005–2007 vs. 2012–2014	
	Women	Men	P	Women	Men	P	Women	Men
Age < 55 years	1738 (7.5%)	6162 (18.6%)	< 0.05	1647 (6.4%)	5468 (13.3%)	< 0.05	< 0.05	< 0.05
Age ≥ 7 years	11208 (48.3%)	8746 (26.4%)	< 0.05	12098 (47.4%)	11571 (28.1%)	< 0.05	< 0.05	< 0.05
Hypertension	17908 (77.2%)	22792 (68.8%)	< 0.05	20568 (80.5%)	31219 (75.9%)	< 0.05	< 0.05	< 0.05
Diabetes	8180 (35.3%)	9623 (23.7%)	< 0.05	7865 (37.3%)	11999 (29.2%)	< 0.05	< 0.05	< 0.05
Hyperlipidemia	10182 (43.9%)	11264 (43.6%)	0.43	1446 (44.1%)	18067 (43.9%)	0.67	0.67	0.33
Current smoking	2403 (10.4%)	10595 (32.0%)	< 0.05	3340 (13.1%)	10989 (26.7%)	< 0.05	< 0.05	< 0.05
Obesity	5879 (25.4%)	5143 (15.5%)	< 0.05	6391 (25.0%)	7807 (19.0%)	< 0.05	0.40	< 0.05
Prior MI	5899 (25.4%)	10097 (30.5%)	< 0.05	5681 (22.2%)	10728 (26.1%)	< 0.05	< 0.05	< 0.05
Prior PCI	736 (3.2%)	1680 (5.1%)	< 0.05	4301 (16.8%)	8534 (20.8%)	< 0.05	< 0.05	< 0.05
Prior CABG	1321 (5.7%)	2764 (8.3%)	< 0.05	1092 (4.3%)	2755 (6.7%)	< 0.05	< 0.05	< 0.05

CABG — coronary artery bypass grafting; MI — myocardial infarction; PCI — percutaneous coronary intervention

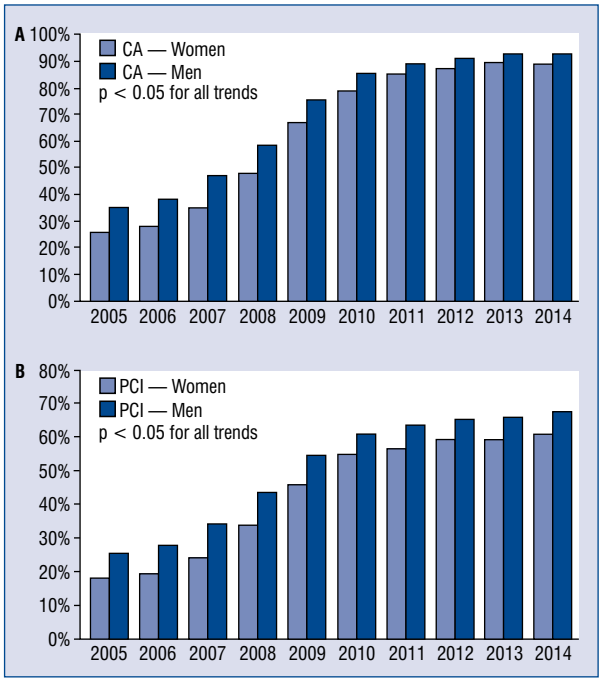

Figure 1. Temporal trends in utilization of coronary angiography (CA) (**A**) and percutaneous coronary intervention (PCI) (**B**).

among the age groups diminished during the study, a slight disproportion still existed. In all age groups, invasive strategies were more widespread in men than in woman. Nevertheless, this disproportion has decreased in recent years (Fig. 2).

There have been significant changes in pharmacotherapy over the last decade, especially in the use of antiplatelet agents. The utilization of P2Y12-receptor blockers substantially increased from 51.0% in women and 59.1% in men from 2005 to 2007 to 92.9% in women and 93.2% in men ($p < 0.05$). Ticlopidine, which was commonly used, was almost completely substituted by clopidogrel. In addition, during the last years a continuous shift from clopidogrel to ticagrelol or prasugrel was observed.

The management outcomes of NSTEMI patients have improved considerably over the last decade. In the present analysis, the risk of reinfarction was reduced from 4.5% in 2005–2007 to 0.3% in 2012–2014 ($p < 0.05$), and the risk of stroke was reduced from 0.5% in 2005–2007 to 0.2% in 2012–2014 ($p < 0.05$). On the other hand, a side effect of the intensive invasive treatment application was observed, especially in the frequency of

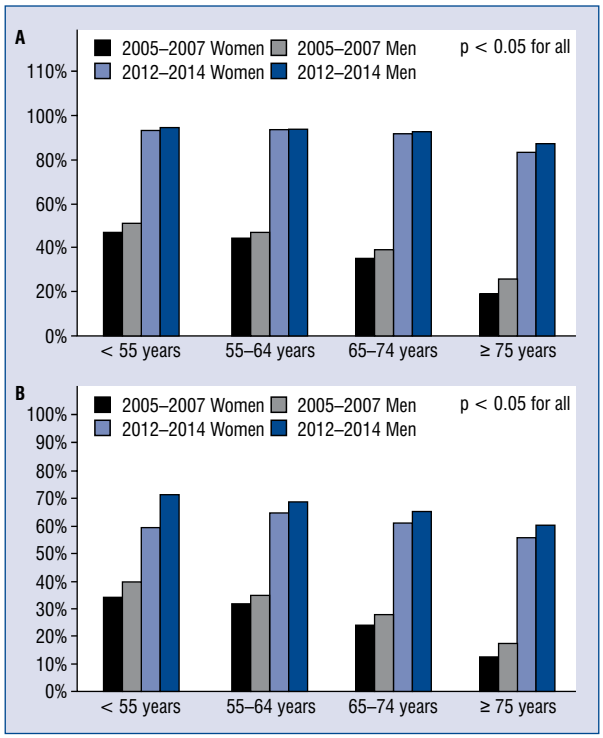

Figure 2. Percentage of coronary angiography (CA) (**A**) and percutaneous coronary intervention (PCI) (**B**) in age groups.

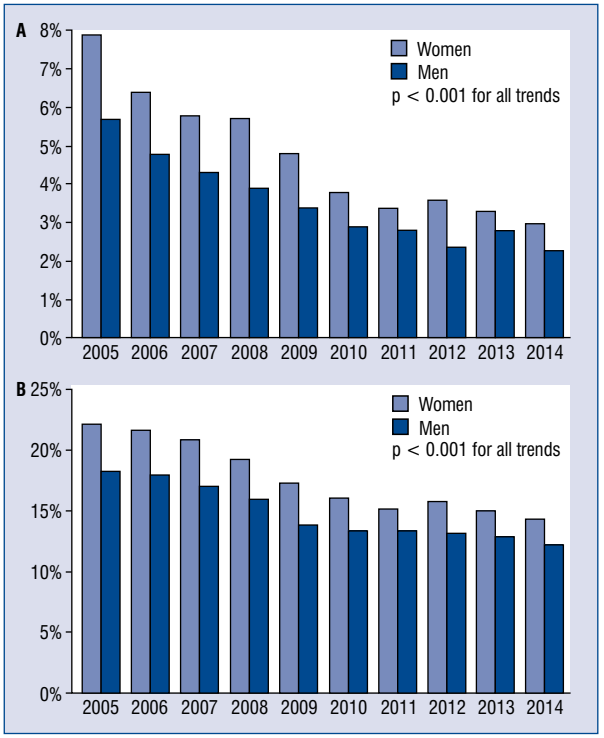

Figure 3. Temporal trends of in-hospital mortality (**A**) and 12-month mortality (**B**).

Table 2. Mortality rates by gender.

Mortality rates	2005–2007			2012–2014			2005–2007 vs. 2012–2014	
	Women	Men	P	Women	Men	P	Women	Men
In-hospital mortality	1541 (6.6%)	1633 (4.9%)	< 0.05	851 (3.3%)	1026 (2.5%)	< 0.05	< 0.05	< 0.05
30-day mortality	2267 (9.8%)	2571 (7.8%)	< 0.05	1686 (6.6%)	2101 (5.1%)	< 0.05	< 0.05	< 0.05
6-month mortality	3988 (17.2%)	4586 (13.8%)	< 0.05	2997 (11.7%)	3994 (9.7%)	< 0.05	< 0.05	< 0.05
12-month mortality	5005 (21.6%)	5897 (17.8%)	< 0.05	3865 (15.1%)	5258 (12.8%)	< 0.05	< 0.05	< 0.05

major bleeding (0.7% in 2005–2007 vs. 1.2% in 2012–2014; $p < 0.05$).

In-hospital mortality decreased by 50% (from 5.6% in 2005–2007 to 2.8% in 2012–2014; $p < 0.05$) and 1-year mortality by up to 30% (from 19.4% in 2005–2007 to 13.7% in 2012–2014; $p < 0.05$) (Fig. 3). These positive tendencies are apparent in all age groups and genders (Table 2). Mortality rates in the four age groups (under 55, 55–64, 65–74, 75 and over) are presented in Figure 4.

A multivariable analysis showed that the impact of the invasive strategy on mortality decrease was immense, with a 3-fold improvement in outcomes in short-term observation and a 2-fold improvement in long-term observation (Tables 3 and 4).

Discussion

The clinical characteristics and management of NSTEMI patients together with treatment

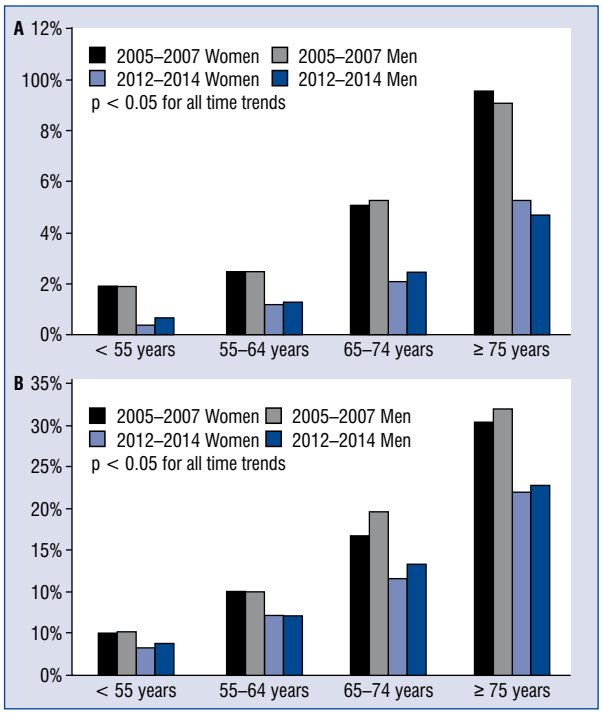

Figure 4. In-hospital mortality (**A**) and 12-month mortality (**B**) in age groups.

outcomes have significantly changed all over the world in recent years [3–5]. In Poland, as in many other countries, NSTEMI has become the most common type of MI.

According to many previous reports on NSTEMI, there are common trends in the baseline clinical profile of patients. The prevalence of major atherosclerosis risk factors like arterial hypertension, diabetes, obesity and chronic kidney disease is still increasing [4, 5]. Similar trends were observed in the present study. Contrary to findings in other countries, the mean age of NSTEMI patients in Poland increased, especially in men. Presumably this is a result of a noticeable smoking decrease and better pharmacological risk factor control, i.e., hypercholesterolemia and arterial hypertension. Over the last 10 years, some important changes in medical therapy have taken place. The vast majority of patients received P2Y12-receptor blockers. Interestingly, from 2005 to 2007 many patients were still administered ticlopidine, which was gradually substituted by clopidogrel and later by new drugs such as ticagrelol, according to the European Society of Cardiology guidelines [1, 2].

Table 3. Multivariate analysis (in-hospital mortality).

	P	OR	OR (95% CI)
Invasive treatment	< 0.0001	0.31	0.31 (0.29–0.33)
Hypercholesterolemia	< 0.0001	0.73	0.73 (0.69–0.77)
Hypertension	< 0.0001	0.73	0.73 (0.69–0.78)
Previous PCI	< 0.0001	0.80	0.80 (0.73–0.88)
Previous CABG	0.0006	0.80	0.80 (0.71–0.91)
Current smokers	0.6776	1.02	1.02 (0.94–1.10)
Female (vs. male)	0.4485	1.02	1.02 (0.97–1.08)
Previous MI	0.0255	1.07	1.07 (1.01–1.14)
Diabetes	0.0021	1.09	1.09 (1.03–1.15)
Time to admission > 12 h	0.0030	1.09	1.09 (1.03–1.16)
LVEF 35–50%	0.0240	1.10	1.10 (1.01–1.20)
ST-T abnormalities in ECG	0.0007	1.16	1.16 (1.07–1.27)
Obesity	< 0.0001	1.18	1.18 (1.10–1.26)
No sinus rhythm in ECG	< 0.0001	1.19	1.19 (1.12–1.27)
Age (on each decade)	< 0.0001	1.63	1.63 (1.59–1.68)
LVEF < 35%	< 0.0001	2.31	2.31 (2.11–2.53)
Prehospital cardiac arrest	< 0.0001	2.37	2.37 (2.09–2.69)
Killip 3 class	< 0.0001	3.67	3.67 (3.41–3.94)
IABP	< 0.0001	3.89	3.89 (3.23–4.69)
Killip 4 class	< 0.0001	13.17	13.2 (12.0–14.4)

CABG — coronary artery bypass grafting; CI — confidence interval; ECG — electrocardiogram; IABP — intraaortic balloon pump; LVEF — left ventricular ejection fraction; MI — myocardial infarction; OR — odds ratio; PCI — percutaneous coronary intervention

Table 4. Multivariate analysis (12-month mortality).

	P	OR	OR (95% CI)
Invasive treatment	< 0.0001	0.51	0.51 (0.49–0.52)
Hypercholesterolemia	< 0.0001	0.81	0.81 (0.79–0.83)
Previous CABG	< 0.0001	0.84	0.84 (0.80–0.88)
Hypertension	< 0.0001	0.85	0.85 (0.83–0.88)
Previous PCI	< 0.0001	0.90	0.90 (0.87–0.94)
Female (vs. male)	< 0.0001	0.94	0.94 (0.92–0.97)
Obesity	0.37	0.99	0.99 (0.96–1.02)
Time to admission > 12 h	0.02	1.02	1.03 (1.00–1.06)
Current smokers	0.0005	1.07	1.06 (1.03–1.10)
Previous MI	< 0.0001	1.12	1.12 (1.09–1.15)
ST-T abnormalities in ECG	< 0.0001	1.14	1.15 (1.11–1.19)
No sinus rhythm in ECG	< 0.0001	1.15	1.14 (1.11–1.18)
Diabetes	< 0.0001	1.29	1.29 (1.26–1.32)
LVEF 35–50%	< 0.0001	1.52	1.52 (1.47–1.57)
Age (on each decade)	< 0.0001	1.57	1.57 (1.55–1.59)
Prehospital cardiac arrest	< 0.0001	1.74	1.74 (1.63–1.85)
Killip 3 class	< 0.0001	1.98	1.98 (1.91–2.06)
IABP	< 0.0001	2.17	2.17 (1.99–2.38)
LVEF < 35%	< 0.0001	2.67	2.67 (2.57–2.78)
Killip 4 class	< 0.0001	4.48	4.48 (4.26–4.71)

CABG — coronary artery bypass grafting; CI — confidence interval; ECG — electrocardiogram; IABP — intraaortic balloon pump; LVEF — left ventricular ejection fraction; MI — myocardial infarction; OR — odds ratio; PCI — percutaneous coronary intervention

The European Society of Cardiology-recommended implementation of a routine invasive strategy has been the most important change in NSTEMI treatment over the last 10 years [1, 2]. A rapid increase in the number of 24/7 catheterization centers in Poland (up to 150) enabled the successful introduction of this recommendation. The percentage of CAs as well as PCIs in NSTEMI patients in Poland reached the same level as countries in Western Europe such as France [4] and Denmark [6] as well as the United States [5]. Importantly, previously reported underutilization of an invasive strategy in women as well as in older patients was not as pronounced in Poland [7–11]. The significant advances in treatment have resulted in a spectacular decrease in mortality rates at an even higher rate than in previous analyses [3–5, 12, 13].

In the multivariable analysis, the invasive strategy was the most important factor contributing to a better prognosis for in-hospital and 12-month observations. The advantages of invasive treatment were apparent in all patients regardless of age or gender. The final results are comparable to data from other countries that have successfully introduced contemporary guidelines [14].

Limitations of the study

This study has several limitations. PL-ACS is a voluntary, observational study, and not all hospitals treating NSTEMI in Poland participated in data collection. The present analysis was retrospective, and some potentially important parameters might not be included. Finally, this is a single country study; therefore, some trends should be interpreted with caution.

Conclusions

In Poland, outcomes of NSTEMI patients have improved substantially over the last 10 years due to the implementation of routine invasive treatment. The invasive approach was beneficial to all age groups and both genders.

Conflict of interest: None declared

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VIA MEDICA

ORIGINAL ARTICLE

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Randomized controlled clinical trials versus real-life atrial fibrillation patients treated with oral anticoagulants. Do we treat the same patients?

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Abstract

Background: *The aim of the study was to compare clinical characteristics of real-life atrial fibrillation (AF) patients with populations included in randomized clinical trials (ROCKET AF and RE-LY).*

Methods: *The analysis included 3528 patients who are participants of the ongoing, multicentre, retrospective CRAFT study. The study is registered in ClinicalTrials.gov: NCT02987062. The study is based on a retrospective analysis of hospital records of AF patients treated with vitamin K antagonists (VKAs) (acenocoumarol, warfarin) and non-vitamin K oral anticoagulants (NOACs) (dabigatran, rivaroxaban). $CHADS_2$ score was used for risk of stroke stratification.*

Results: *VKA was prescribed in 1973 (56.0%), while NOAC in 1549 (44.0%), including dabigatran — 504 (14.3%) and rivaroxaban — 1051 (29.8%), of the 3528 patients. VKA patients in the CRAFT study were at significantly lower risk of stroke ($CHADS_2$ 1.9 ± 1.3), compared with the VKA population from the RE-LY (2.1 ± 1.1) and the ROCKET-AF (3.5 ± 1.0). Patients in the CRAFT study treated with NOAC ($CHADS_2$ for patients on dabigatran 150 mg — 1.3 ± 1.2 and on rivaroxaban — 2.2 ± 1.4) had lower risk than patients from the RE-LY (2.2 ± 1.2) and the ROCKET AF (3.5 ± 0.9).*

Conclusions: *Real-world patients had a lower risk of stroke than patients included in the RE-LY and ROCKET AF trials.* (Cardiol J 2020; 27, 5: 590–599)

Key words: non-valvular atrial fibrillation, oral anticoagulation, randomized trial, real-world study

Introduction

Atrial fibrillation (AF) is an increasingly common cardiac arrhythmia which affects 3% of adults in the European population [1]. It is related to the ageing of modern societies and its prevalence is increasing with a presence of certain comorbidities (i.e. hypertension, coronary artery disease, heart failure) [1, 2]. A key element of AF patient management is anticoagulation to prevent thromboembolic events, especially AF-related stroke, which is combined with poor outcomes and high total costs [1]. According to the current European Society of Cardiology (ESC) guidelines for non-valvular AF treatment, the first line drugs are non-vitamin K oral anticoagulants (NOACs), which are preferred over vitamin K antagonists (VKA) [1]. NOACs were shown to be at least as effective and safer than VKAs for stroke prevention in patients with non-valvular AF [1]. However, it is not clearly confirmed, how the success of NOACs' approval trials — ROCKET AF (rivaroxaban), RE-LY (dabigatran

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etexilate), and ARISTOTLE (apixaban) may reflect on real-life clinical practice.

The aim of the study was to compare clinical characteristics of real-life AF patients with populations included in randomized clinical trials (ROCKET AF and RE-LY).

Methods

The analysis was based on multicenter, retrospective CRAFT (MultiCenter expeRience in AFib patients Treated with OAC) study, registered in ClinicalTrials.gov: NCT02987062 [3]. The CRAFT study was conducted at two cardiology centers in Poland, academic center located in capital city and district hospital. The study was approved by a local ethical review board.

Study design and population

The CRAFT study retrospectively included all patients hospitalized in the years between 2011 and 2016 with diagnosis of non-valvular AF and treated with one of the oral anticoagulants (OAC) — VKAs (acenocoumarol, warfarin) and NOAC (apixaban, dabigatran, rivaroxaban). Patients were 18 years of age and older. There were no other specific inclusion or exclusion criteria. Patients on apixaban were excluded due to a small number in this group. Another NOAC — edoxaban was not available on the Polish market at the time of data collection. The data about patient characteristics was gathered retrospectively from hospital records.

Design of the randomized trials

The Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study was a multicenter, randomized trial designed to compare two fixed doses of dabigatran (110 mg or 150 mg) with adjusted-dose warfarin [4]. The Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) was a multicenter, randomized, double-blind trial, in which patients were randomly assigned to receive a fixed dose rivaroxaban (20 mg daily or 15 mg daily in patients with a creatinine clearance of 30 to 49 mL per minute) or adjusted--dose warfarin [5]. In both trials patients with non--valvular AF documented on electrocardiography who were at increased risk of stroke, which was defined as history of previous stroke or transient ischemic attack (TIA) or systemic embolism, older age, coexistence of comorbidities such as heart failure with reduced ejection fraction, hypertension, diabetes mellitus or coronary artery diseases were randomized to different study arms. Complete inclusion and exclusion criteria are described in trial protocols [5, 6]. The main exclusion criteria are shown in Table 1.

Comparative analysis of patients treated with OAC — randomized trials vs. real-world patients

In the current analysis, patients were divided into four groups according to the type of OAC (VKA, dabigatran 110 mg, dabigatran 150 mg, rivaroxaban 15 mg or 20 mg). Investigators compared clinical characteristics of real-life AF patients from the CRAFT study with populations included in the randomized clinical trials (ROCKET AF and RE-LY). Patients were compared in terms of baseline characteristics regarding demographics, medical history, type of AF (paroxysmal, persistent or permanent), diagnostic test results and co-pharmacotherapy. Thromboembolic risk of each group was compared using $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥ 75, Diabetes, Stroke [doubled]) score which was used in the ROCKET AF and RE-LY trials.

Statistical analysis

Statistical analyses were performed using SPSS software, version 22 (IBM SPSS Statistics 22, USA, New York). Normally distributed continuous variables were presented as mean values and standard deviations, while ordinal variables and non-normally distributed continuous variables, as median values and interquartile ranges (IQR). Categorical data is presented as a number of patients and percentages. The significance of differences between groups was determined by the Fisher exact test for categorical variables and Mann-Whitney U test for continuous and ordinal variables, respectively. P-values less than 0.05 were considered significant. All tests were two-tailed.

Results

Characteristics of the study patients

A comparison of clinical characteristics of patients from the CRAFT, RE-LY and ROCKET AF studies are presented in Table 2. Table 3 presents thromboembolic risk factors in the study participants according to the treatment group. In both trials (RE-LY and ROCKET AF) patients with creatinine clearance < 30 mL per minute were excluded, while in the present study 2.7% of patients were below this threshold.

Table 1. The main exclusion criteria for the randomized trials.

RE-LY	ROCKET-AF
1. History of heart valve disorder (i.e., prosthetic valve or hemodynamically relevant valve disease).	1. Hemodynamically significant mitral valve stenosis. Prosthetic heart valve.
2. Severe, disabling stroke within the previous 6 months, or any stroke within the previous 14 days.	2. Reversible causes of atrial fibrillation. Planned cardioversion.
3. Conditions associated with an increased risk of bleeding (i.e. history of an active severe bleeding, major surgery within the previous month, planned surgery or intervention, uncontrolled hypertension, recent malignancy or radiation therapy).	3. Known presence of atrial myxoma or left ventricular thrombus.
4. Anemia (hemoglobin level less than 100 g/L) or thrombocytopenia.	4. Conditions associated with an increased risk of bleeding (i.e. history of an internal bleeding, planned invasive procedure, sustained uncontrolled hypertension).
5. Contraindication to warfarin treatment.	5. Anemia (hemoglobin < 10 g/dL), platelet count < 90,000/μL.
6. Reversible causes of atrial fibrillation.	6. Severe, disabling stroke within 3 months or any stroke within 14 days. TIA within 3 days.
7. Plan to perform a pulmonary vein ablation or surgery for cure of the atrial fibrillation.	7. Indication for anticoagulant therapy for a condition other than atrial fibrillation (e.g. venous thromboembolism).
8. Severe renal impairment (estimated creatinine clearance 30 mL/min or less).	8. Treatment with: ASA > 100 mg daily; or ASA in combination with thienopyridines, intravenous antiplatelets or fibrinolytics within 10 days before randomization.
9. Active liver disease.	9. Anticipated need for chronic treatment with a non-steroidal anti-inflammatory drug.
10. Active infective endocarditis.	10. Drug addiction or alcohol abuse.
11. Women who are pregnant or of childbearing potential.	11. Known allergy or hypersensitivity to any component of rivaroxaban, warfarin or placebo excipients.
	12. Calculated creatinine clearance < 30 mL/min.
	13. Known significant liver disease.
	14. Active endocarditis.
	15. Pregnancy or breast-feeding.

The table was prepared based on trial protocols; ASA — acetylsalicylic acid; TIA — transient ischemic attack

CRAFT study

A total of 3528 Caucasian patients were enrolled in the CRAFT study, of whom 1973 (56.0%) were on VKAs and 1549 (44.0%) patients were on NOACs, including rivaroxaban — 1051 (29.8%) and dabigatran — 504 (14.3%). In the dabigatran group, 187 (5.3%) patients received 110 mg twice daily and 311 (8.8%) patients received 150 mg twice daily. There were 6 patients with missing data on the dabigatran dose. Patients on rivaroxaban received 15 mg or 20 mg once daily, but following the methodology from the ROCKET AF trial, both doses were analyzed collectively. Figure 1 shows the flow chart of patient selection in the current study. The mean age of the total population was 67.9 ± 13.2 years and 59.8% were male. Patients on dabigatran 110 mg were the oldest (75.8 ± 10.2 years). In the total population paroxysmal AF had 1820 (51.6%), permanent AF — 955 (27.0%) and persistent — 596 (16.9%) patients.

RE-LY trial

In the RE-LY study a total cohort of 18,113 patients were enrolled, including 6022 patients on VKA, 6015 on dabigatran 110 mg and 6076 on dabigatran 150 mg. The mean age of the total cohort was 71 years and 63.6% were male [4].

ROCKET AF trial

In the ROCKET AF study, a total of 14,264 patients were enrolled, including 7133 patients on VKA and 7131 on rivaroxaban (15 or 20 mg dose). Reduced dose of rivaroxaban (15 mg once daily) was intended for patients with estimated creatinine clearance 30–49 mL/min (calculated by the Cockroft-Gault formula). The mean age of the

Table 2. Baseline characteristics of the study participants (from the CRAFT, RE-LY [2] and ROCKET AF studies [3]) according to the treatment group.

Variable	VKA				Dabigatran 110 mg			Dabigatran 150 mg			Rivaroxaban 15 or 20 mg		
	CRAFT (n = 1973)	RE-LY (n = 6022)	ROCKET AF (n = 7133)	P*	CRAFT (n = 187)	RE-LY (n = 6015)	P	CRAFT (n = 311)	RE-LY (n = 6076)	P	CRAFT (n = 1051)	ROCKET AF (n = 7131)	P
Age [years]	67.0 ± 12.8	71.6 ± 8.6	73.0 ± 9.6	< 0.0001 < 0.0001	75.8 ± 10.2	71.4 ± 8.6	< 0.0001	60.0 ± 12.4	71.5 ± 8.8	< 0.0001	70.5 ± 13.1	73.0 ± 9.6	< 0.0001
Male sex	1252 (63.5)	3809 (63.3)	4301 (60.3)	0.87 0.01	105 (56.1)	3865 (64.3)	0.02	198 (63.7)	3840 (63.2)	0.86	548 (52.1)	4300 (60.3)	< 0.0001
BMI [kg/m^2]	29.6 ± 6.3, n = 125	–	28.1 ± 5.0	0.001	28.0 ± 5.4, n = 53	–		28.5 ± 4.8, n = 37	–		29.3 ± 4.9, n = 146	28.3±5.1	0.02
Persistent AF	351/1902 (18.5)	1930/6021 (32.0)	5762 (80.8)	< 0.0001 < 0.0001	28/182 (15.4)	1950/6011 (32.4)	< 0.0001	83/298 (27.9)	1909/6075 (31.4)	0.20	134/998 (13.6)	5786 (81.1)	< 0.0001
Paroxysmal AF	990/1901 (52.1)	2036/6021 (33.8)	1269 (17.8)	< 0.0001 < 0.0001	86/182 (47.3)	1929/6011 (32.1)	< 0.0001	178/298 (59.7)	1978/6075 (32.6)	< 0.0001	566/987 (57.3)	1245 (17.5)	< 0.0001
Permanent AF	561/1902 (29.5)	2055/6021 (34.1)	–	0.0002	68/182 (37.4)	2132/6011 (35.4)	0.58	37/298 (12.4)	2188/6075 (36.0)	< 0.0001	289/988 (29.3)	–	
ASA	304 (15.4)	2442/6017 (40.6)	2619 (36.7)	< 0.0001 < 0.0001	17/187 (9.1)	2404/6013 (40.0)	< 0.0001	13/311 (4.2)	2352/6075 (38.7)	< 0.0001	88/1050 (8.4)	2586 (36.3)	< 0.0001
ACEI or ARB	1221/1632 (74.8)	3939/6017 (65.5)	–	< 0.0001	82/108 (75.9)	3987/6013 (66.3)	0.04	157/244 (64.3)	4053/6075 (66.7)	0.44	485/676 (71.7)	–	
BB	1342/1631 (82.3)	3719/6017 (61.8)	–	< 0.0001	88/108 (81.5)	3784/6013 (62.9)	< 0.0001	182/244 (74.6)	3872/6075 (63.7)	< 0.0001	540/676 (79.9)	–	
Amiodarone	162/1971 (8.2)	644/6017 (10.7)	–	0.001	20/186 (10.8)	624/6013 (10.4)	0.86	27/311 (8.7)	665/6075 (10.9)	0.22	110/1050 (10.5)	–	
Statin	1046/1632 (64.1)	2673/6017 (44.4)	–	< 0.0001	72/108 (66.7)	2698/6013 (44.9)	< 0.0001	120/244 (49.2)	2667/6075 (43.9)	0.10	439/676 (64.9)	–	

Continuous variables are presented as mean ± standard deviation or number and (percentage).
ACEI — angiotensin-converting enzyme inhibitor; AF — atrial fibrillation; ARB — angiotensin-receptor blocker; ASA — acetylsalicylic acid; BB — beta-blocker; BMI — body mass index; n — number; CRAFT — MultiCenter expeRience in AFib patients Treated with OAC; RE-LY — The Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET — Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation, VKA — vitamin K antagonist
*First p-value, (written above) refers to the comparison of VKA patients from the CRAFT and RE-LY studies, second p-value (written below) refers to the comparison of patients from the CRAFT and ROCKET AF studies.

Table 3. Thromboembolic risk factors in the study participants (from the CRAFT, RE-LY [2] and ROCKET AF studies [3]) according to the treatment group.

Variable	VKA				Dabigatran 110 mg			Dabigatran 150 mg			Rivaroxaban 15 or 20 mg		
	CRAFT (n = 1973)	RE-LY (n = 6022)	ROCKET AF (n = 7133)	P*	CRAFT (n = 187)	RE-LY (n = 6015)	P	CRAFT (n = 311)	RE-LY (n = 6076)	P	CRAFT (n = 1051)	ROCKET AF (n = 7131)	P
Previous stroke or TIA	219/1960 (11.2)	1195 (19.8)	3895 (54.6)	< 0.0001 < 0.0001	35/185 (18.9)	1195/6015 (19.9)	0.74	24/309 (7.8)	1233 (20.3)	< 0.0001	168/1046 (16.1)	3916 (54.9)	< 0.0001
$CHADS_2$ score	1.9 ± 1.3, n = 1960	2.1 ± 1.1	3.5 ± 1.0	< 0.0001 < 0.0001	2.6 ± 1.2, n = 185	2.1 ± 1.1	< 0.0001	1.3 ± 1.2, n = 309	2.2 ± 1.2	< 0.0001	2.2 ± 1.4, n = 1046	3.5 ± 0.9	< 0.0001
0–1	886/1960 (45.2)	1859 (30.9)	–	< 0.0001	32/185 (17.3)	1958/6014 (32.6)	< 0.0001	208/309 (67.3)	1958 (32.2)	< 0.0001	365/1046 (34.9)	–	< 0.0001
2	475/1960 (24.2)	2230 (37.0)	934 (13.1)	< 0.0001 < 0.0001	63/185 (34.1)	2088/6014 (34.7)	0.87	62/309 (20.1)	2137 (35.2)	< 0.0001	279/1046 (26.7)	925 (13.0)	< 0.0001
3–6	599/1960 (30.6)	1933 (32.1)	6197 (86.9)	0.22 < 0.0001	90/185 (48.6)	1968/6014 (32.7)	< 0.0001	39/309 (12.6)	1981 (32.6)	< 0.0001	402/1046 (38.4)	6205 (87.0)	< 0.0001
Vascular disease**	862/1960 (44.0)	968 (16.1)	1724 (24.2)	<0.0001 <0.0001	106/185 (57.3)	1008/6015 (16.8)	< 0.0001	67/309 (21.7)	1029 (16.9)	0.03	504/1046 48.2)	1583 (22.2)	< 0.0001
Heart failure	709/1960 (36.2)	1922 (31.9)	4441 (62.3)	0.0004 < 0.0001	99/185 (53.5)	1937/6015 (32.2)	< 0.0001	62/309 (20.1)	1934 (31.8)	< 0.0001	434/1046 (41.5)	4467 (62.6)	<0.0001
Diabetes mellitus	518/1960 (26.4)	1410 (23.4)	2817 (39.5)	0.01 < 0.0001	49/185 (26.5)	1409/6015 (23.4)	0.33	51/309 (16.5)	1402 (23.1)	0.01	309/1046 (29.5)	2878 (40.4)	< 0.0001
Hypertension	1407/1960 (71.8)	4750 (78.9)	6474 (90.8)	< 0.0001 < 0.0001	136/185 (73.5)	4738/6015 (78.8)	0.08	207/309 (67.0)	4795 (78.9)	< 0.0001	748/1046 (71.5)	6436 (90.3)	< 0.0001
COPD	160/1970 (81.0)	–	743 (10.4)	< 0.0001	23/187 (12.3)	–		8/310 (2.6)	–		134/1050 (12.8)	754 (10.6)	0.03

Continuous variables are presented as mean ± standard deviation or number and (percentage).
CHADS — congestive heart failure, hypertension, age (≥ 75 years), diabetes mellitus, stroke or transient ischemic attack; COPD — chronic obstructive pulmonary disease; n — number; CRAFT — Multi-Center expeRience in AFib patients Treated with OAC; RE-LY — The Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET — Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; TIA — transient ischemic attack; VKA — vitamin K antagonist
*First p-value, (written above) refers to the comparison of VKA patients from the CRAFT and RE-LY studies, second p-value (written below) refers to the comparison of patients from the CRAFT and ROCKET AF studies.
**In the CRAFT study "Vascular disease" was defined as prior myocardial infarction, ischemic heart disease, peripheral artery disease or aortic plaque, while in the RE-LY and ROCKET AF studies only prior myocardial infarction was consider.

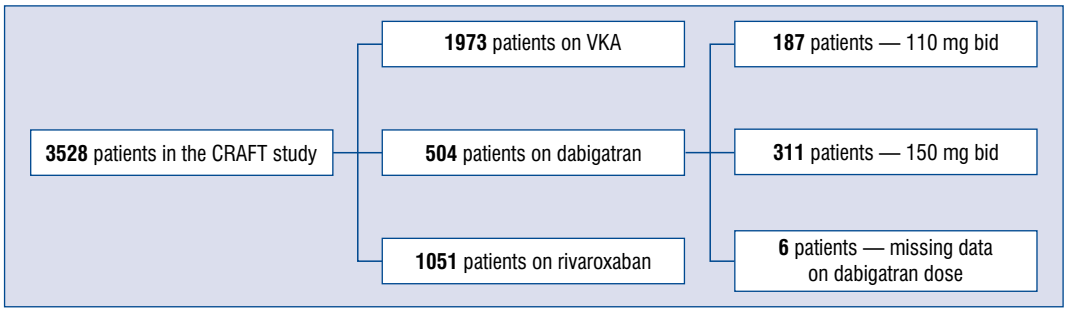

Figure 1. Flow chart of patient enrollment in the current analysis; bid — twice daily, CRAFT — MultiCentre expeRience in AFib patients Treated with OAC; VKA — vitamin K antagonists.

total cohort was 73.0 ± 9.6 years and 60.3% were male [5].

Comparative analysis of patients treated with OAC — randomized trials vs. real-world patients

VKA patients

Patients on VKAs in the CRAFT study were younger (67.0 ± 12.8 years) than patients from the RE-LY and ROCKET AF trials (71.6 ± 8.6 years, $p < 0.0001$; and 73.0 ± 9.6, $p < 0.0001$, respectively). Patients in the CRAFT study (similar to the RE-LY study) were more likely to be male (63.5%) than in the ROCKET AF (60.3%, $p = 0.01$). In the CRAFT study patients on VKAs had mainly paroxysmal AF (52.1%), in the ROCKET AF had persistent AF (80.8%), while in the RE-LY comparably often all types of AF. Patients in the present study had significantly lower risk of stroke ($CHADS_2$ 1.9 ± 1.3), compared with VKA population from RE-LY (2.1 ± 1.1) and ROCKET AF (3.5 ± 1.0). A comparison of thromboembolic risk (assessed by $CHADS_2$ score) of each group from CRAFT, RE-LY and ROCKET AF studies is presented in Figure 2. Patients on VKAs in the ROCKET AF trial more frequently had a history of stroke or TIA, heart failure, diabetes, hypertension and chronic pulmonary disease than in the CRAFT study. Whereas, patients from the RE-LY trial more frequently had a history of stroke or TIA and hypertension, but less frequently had heart failure or diabetes than in the CRAFT study.

Dabigatran patients

Patients on dabigatran 110 mg in the CRAFT study were older (75.8 ± 10.2 years) and were less frequently male (56.1%), compared with patients on the same dose in the RE-LY trial (71.4 ± 8.6 years, $p < 0.0001$; 64.3%, $p = 0.02$). In the CRAFT study patients on dabigatran 110 mg had mainly paroxysmal AF (47.3%), while in the RE-LY trial comparably often had all types of AF. There was no statistical significance in comparison of permanent AF occurrence between CRAFT and RE-LY studies. Patients on dabigatran 110 mg in the CRAFT study were at higher risk of stroke ($CHADS_2$ 2.6 ± ± 1.2) compared with dabigatran 110 mg population from the RE-LY trial (2.1 ± 1.1). Patients on dabigatran 110 mg in the CRAFT study also had heart failure more frequently, but had similarly frequent previous stroke or TIA, diabetes and hypertension.

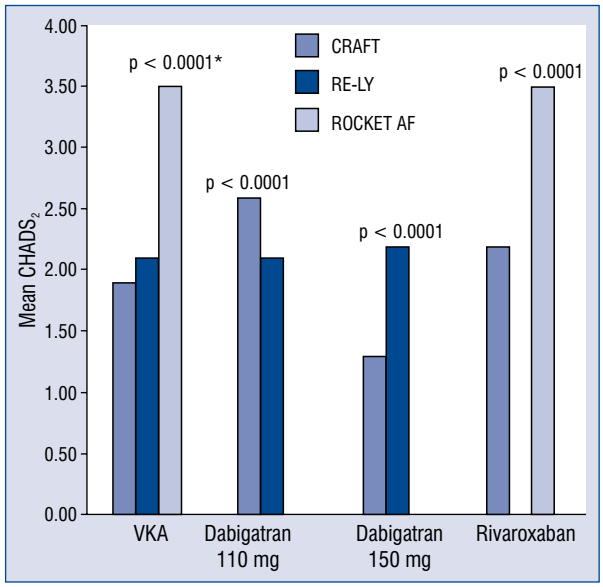

Figure 2. Thromboembolic risk basing on $CHADS_2$ score in different oral anticoagulants groups. Results are shown as mean value. *Significant difference ($p < 0.05$) where observed for comparison of vitamin K antagonists (VKAs) patients from the CRAFT study with both RE-LY and ROCKET AF trials.

Patients on dabigatran 150 mg in the CRAFT study were younger (60.0 ± 12.4 years), than patients on the same dose in the RE-LY trial (71.5 ± ± 8.8 years, $p < 0.0001$). In the CRAFT study patients on dabigatran 150 mg had mainly paroxysmal AF (59.7%), while in the RE-LY trial had mainly permanent AF (36.0%). Patients on dabigatran 150 mg in the CRAFT study had a lower risk of stroke ($CHADS_2$ 1.3 ± 1.2) when compared to patients from the RE-LY trial (2.2 ± 1.2). Patients on dabigatran 150 mg in the CRAFT study frequently had less previous stroke or TIA, heart failure, diabetes and hypertension than in the RE-LY trial. There was no difference with regard to sex and persistent AF occurrence between groups.

Rivaroxaban patients

Patients on rivaroxaban in the CRAFT study were younger (70.5 ± 13.1 years) and less frequently male (52.1%), when compared with patients from the ROCKET AF trial (73.0 ± 9.6 years, $p < 0.0001$; 60.3%, $p < 0.0001$). In the CRAFT study patients on rivaroxaban more frequently had paroxysmal AF (57.3%), while in the ROCKET AF trial they had persistent AF (81.1%). Patients on rivaroxaban in the present study had a significantly lower risk of stroke ($CHADS_2$ 2.2 ± 1.4), compared with the population from ROCKET AF (3.5 ± 0.9). Patients on rivaroxaban in the CRAFT study had previous stroke or TIA, heart failure, diabetes and hypertension less frequently than in the ROCKET AF trial, but more often had chronic obstructive pulmonary disease.

Discussion

Randomized controlled trials (RCT) are the gold standard for evaluation of therapy outcomes in terms of treatment efficacy and safety [7]. However, it needs to be emphasized that they have a limited generalizability because they are performed under very different conditions from a routine clinical practice [7]. Rigorous insight into those differences in patient characteristics may be important in interpreting results of RCT. Therefore, there is a need for real-life data to compare populations enrolled to RCT with patients from everyday clinical practice. It should however, be underlined that RCT and real-word studies are complementary. They provide data from different settings and both contribute to knowledge on AF patients.

Therapy with VKAs is found to be highly effective for stroke prevention in non-valvular AF patients, however a proper monitoring and dose adjustment is challenging for physicians and patients [8, 9]. What is more, the efficacy and safety of VKAs depends on inter- and intra-individual variations, which are associated with food and drug interactions [8, 9]. On the other hand, NOACs are available with no need for regular blood monitoring and have fewer interactions with other medications [10, 11]. However, one third of patients treated with NOACs appear to have disruptions in therapy, which are associated with 4–6-fold increased risk of stroke or TIA [12]. The ESC guidelines for non-valvular AF treatment recommend NOACs as the first line drugs [1], especially for patients on VKAs with unsatisfactory individual time in therapeutic range (TTR). Data from smaller studies showed that NOACs are safe and effective in real-world non-valvular AF patients also in secondary stroke prevention [13–15].

Our understanding of rivaroxaban (direct oral factor Xa inhibitor) and dabigatran (direct thrombin inhibitor) efficacy and safety profiles mainly come from the two RCTs — ROCKET AF and RE-LY, respectively [4, 5]. In ROCKET AF rivaroxaban was non-inferior to warfarin in the prevention of stroke or systemic embolism, with no significant differences in incidence of overall bleeding events between groups, though it was associated with a lower rate of intracranial and fatal bleedings [5]. In the RE-LY trial, the 150-mg dose of dabigatran was associated with lower rates of stroke and systemic embolism, and a similar rate of major hemorrhage [4]. Whereas, the 110-mg dose of dabigatran was associated with similar rates of stroke and systemic embolism and lower rates of major hemorrhage [4].

Importantly, the CRAFT study revealed a lower incidence of previous stroke or TIA in the real-world, than was observed in the RCTs. The difference was especially remarkable in comparison with the ROCKET AF trial, where more than half of the population (54.9%) experienced previous stroke or TIA [5], while in the CRAFT study it was only 12.7%. The present results are not isolated, and they are in line with a recently performed prospective, observational Xarelto for Prevention of Stroke in Patients With Atrial Fibrillation (XANTUS) study, where 19% of patients with non-valvular AF experienced previous stroke or TIA [16]. The aim of this study was to assess rivaroxaban in stroke prevention in real-life clinical practice. The mean age of the cohort in the XANTUS study was 71.5 ± 10 years, 41% were female and there was a higher proportion of paroxysmal AF [16], similar to the population of this study.

Patients in the CRAFT study had paroxysmal AF significantly more often, while patients in the RE-LY and ROCKET AF trials had more sustained forms [4, 5]. These results are in line with data from Atrial Fibrillation General Pilot registry conducted by ESC, which showed that Polish patients more often had paroxysmal AF (32.8%) than patients from other countries of the European Union (25.5%) [17]. It is known that more sustained forms of AF may be associated with increased symptoms and cardiovascular morbidity [18]. The prevailing frequency of paroxysmal AF and thus a lower burden of comorbidities, was probably associated with a lower estimated thromboembolic risk in patients from the CRAFT and XANTUS studies. Moreover, Gorczyca-Michta and Wożakowska-Kapłon [19] revealed that paroxysmal arrhythmia is a factor associated with an increased probability of NOAC prescription.

In the CRAFT study patients had a lower risk of stroke (calculated by $CHADS_2$ score) than patients included in the RE-LY and ROCKET AF trials, as showed in Figure 2. This was similarly observed in a retrospective REal-LIfe Evidence on stroke prevention in patients with atrial Fibrillation (RELIEF), a study evaluating the use of rivaroxaban in a German community [20]. In this study risk of stroke in non-valvular AF patients was similar to rivaroxaban (mean $CHADS_2$ 1.7) and VKA (mean $CHADS_2$ 1.8) patients as in the present study [20]. These data showed that real-world patients have a lower risk of stroke than patients included in RCT, especially when compared to the ROCKET AF trial. Nevertheless, as previously observed in the CRAFT study, there were differences in clinical characteristics of AF patients treated with OAC between the district and academic hospitals. Patients treated in an academic hospital were younger, had lower $CHADS_2$, CHA_2DS_2VASc scores, had less comorbidities and a lower risk of bleeding complications than patients treated in the district hospital [21]. It should be noted, that a majority of the CRAFT population was recruited in an academic hospital and nearly 75% of this group patients were relatively low risk and were admitted to hospital for AF ablation or cardioversion.

However, in the ROCKET AF rivaroxaban failed to demonstrate a reduction in ischemic stroke in comparison to warfarin. One of the hypotheses had concerns that patients on VKA included in the ROCKET AF study had a mean TTR of approximately 63% [5, 22]. While, data from meta-analysis including patients from everyday practice suggested that real TTR is about 9% lower than in randomized selected patients [23]. Results herein suggest that in real-life clinical practice patients are healthier, with lower thromboembolic risk. Additionally, lower TTR may result in a worse effectiveness of VKA in real-life than was shown in the ROCKET AF. These may translate into additional benefits from the use of NOACs in real-life clinical practice.

Patients enrolled in the CRAFT study were younger and the prevalence of concomitant diseases was lower than in patients from the ROCKET AF trial, as well as the fact that patients were on dabigatran 150 mg in the RE-LY trial [4, 5]. Interestingly, in the CRAFT study only patients on dabigatran 110 mg had a higher risk of stroke (calculated using $CHADS_2$ score) and had a similar frequency of previous stroke or TIA, compared to patients from the RE-LY trial [4]. This real-life cohort was older and had more comorbidities than groups on other anticoagulants. This probably reflects that physicians prescribe a lower dose of dabigatran for elderly and patients suffering from numerous concomitant diseases [24]. Lopatowska et al. [25] did a study based on 1556 real-life Polish AF patients, which observed that the use of OAC increased with higher CHA_2DS_2-VASc score of up to 3 points and surprisingly was less frequent in scores ≥ 4. However, Steinberg et al. [26] showed that elderly AF patients rarely have absolute contraindications to oral anticoagulation therapy albeit those who do are also at high risk for thromboembolic events. It may be a sign that in elderly, anticoagulation therapy is underutilized despite strong indications. Similarly, The Global Anticoagulant Registry in the FIELD-Atrial Fibrillation (GARFIELD-AF) registry demonstrated some inaccuracies. Patients with a low risk of stroke had prescribed anticoagulants more often than needed, while patients with a high risk of stroke were left without this treatment [27]. Moreover, authors of a prospective observational REgistro POliterapie SIMI (REPOSI) study, based on in-patients aged ≥ 65 years, stressed that a proper adherence to the antithrombotic therapy guidelines, among elderly AF patients is associated with a lower risk for all cause and cardiovascular deaths [28].

In a real-life setting the educational level of patients also matters, more than in RCT. Knowledge about AF and its consequences, as well as the importance of uninterrupted anticoagulation therapy, influences adherence to the therapy. It was shown in the OCULUS study that the educational level of patients was unsatisfactory and may translate into further differences in stroke prevention effectiveness [29].

Limitations of the study

The limitations mainly derive from the CRAFT study. First of all, the sample size was not representative of the whole population because data came from just two centers. It should be underlined that rivaroxaban and dabigatran groups enrolled in the CRAFT study were more than ten times less populated than their RCTs counterparts, nonetheless the study included over 3500 patients.

Importantly, based on inclusion criteria of RCT there was an imbalance of thromboembolic risk profile of patients between CRAFT and ROCKET AF studies. In the ROCKET AF trial, only patients with moderate-to-high risk of stroke had been enrolled and, according to the protocol, the proportion of patients with a previous stroke or TIA, was brought up to 50% of the whole study population during the randomization process.

Furthermore, there was no possibility to compare the risk of stroke using a more accurate and valid CHA_2DS_2-VASc classification, because this score was not used in the ROCKET AF or RE-LY trials.

Additionally, a retrospective study may contain inaccuracies such as completeness of data or coding that can result in biases. Moreover, there were a limited number of patients and neither apixaban or edoxaban were available on the market, and were thus excluded from the analysis.

Conclusions

The CRAFT study showed that real-world patients demonstrated a distinct clinical profile compared to populations from the RE-LY and ROCKET AF trials. In general, real-world patients had a lower risk of stroke and prevalence of comorbid diseases than patients included in the RE-LY and ROCKET AF trials. Only patients who received dabigatran 110 mg in the CRAFT study were at higher risk of thromboembolic events than the same group in the RE-LY trial.

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Long term outcomes in diabetic patients treated with atherectomy for peripheral artery disease

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Abstract

Background: *The prevalence of diabetes has increased significantly in well-developed countries during the last decade and it continues to grow. Diabetes increases the risk of restenosis in patients treated percutaneously for peripheral artery disease. The present study sought to compare outcomes of atherectomy treatment in diabetic (DM) vs. non-diabetic (nDM) patients suffering from peripheral artery disease.*

Method: *Between 2008 and 2012, 204 revascularization atherectomy procedures were performed on arteries of the lower extremities. The endpoints included target lesion revascularization (TLR), amputation and death. The type of atherectomy (excisional-soft plaque, orbital-calcified plaque, with active aspiration — with a thrombus) was left to operator discretion.*

Results: *This study contains 132 DM (66% male, age 68 ± 11.2 years) and 72 nDM (63% male, age 75 ± 11.3 years) subjects. DM were younger but had a higher prevalence of coronary artery disease (DM: 91% vs. nDM: 62%, $p < 0.0001$) and end-stage renal disease (DM: 22% vs. nDM: 2.5%, $p < 0.0001$). There were no differences in critical limb ischemia between the groups (DM: 21% vs. nDM: 12%, $p = 0.13$). Mean time of follow-up was 384 and 411 days in DM and nDM, respectively ($p = 0.43$). There were no significant differences in TLR (DM: 15.2% vs. nDM: 22.2%, $p = 0.249$), amputations (DM: 3.0% vs. nDM: 1.5%, p = NS) or death rates (DM: 2.2% vs. nDM: 2.7%, p = NS). Kaplan-Mayer analysis showed no significant differences between the groups in the time to TLR, amputation or death.*

Conclusions: *Plaque modification with adjusted atherectomy appears to have similar outcomes in diabetic as well as in non-diabetic patients. Nonetheless, a randomized study would be warranted to confirm the findings of the current study.* (Cardiol J 2020; 27, 5: 600–607)

Key words: atherectomy, diabetes mellitus, peripheral artery disease, critical limb ischemia, claudication, below the knee, above the knee

Introduction

Diabetes mellitus (DM) has a pandemic status in well-developed countries. It is projected that DM will have a prevalence of 552 million worldwide by 2030 [1]. The strongest risk factors for peripheral artery disease (PAD) are DM and smoking [2]. Whereas the ratio of smokers is falling, the DM prevalence continues to increase. The symptomatic PAD is observed in 21% of patients with DM [3]. Moreover, DM is also an independent risk factor for chronic kidney disease which significantly increases the chance of PAD [4]. Over the years multiple therapies for PAD have emerged, includ-

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ing pharmacological regimens, endovascular and open surgery, drug-coated balloons, and stem cell therapy [5]. Nevertheless, revascularization of lower limb arteries in patients with DM brings disappointing long-term outcomes in comparison to the non-diabetic population [6, 7]. This could be caused by the fact that diabetic lesions in diabetic patients occur over a wider area of the vasculature, including small-diameter vessels [8]. As a result, the atherectomy type chosen based on the plaque morphology and vessel diameter may improve long-term outcomes [9].

The long-term outcomes of endovascular revascularization of lower limb arteries using atherectomy in diabetic patients remains unclear. Therefore, the aim of this study to is compare long-term outcomes after endovascular revascularization of lower limb arteries with atherectomy in diabetic (DM) and non-diabetic (nDM) patients.

Methods

Subjects

This study is based on a retrospective study of 203 consecutive patients with symptomatic PAD who underwent endovascular revascularization with atherectomy between 2008 and 2012 at San Antonio Endovascular and Heart Institute. 132 patients were diabetic, whereas 72 were non-diabetic.

Adult patients (> 18 years old) with both intermittent claudication (Rutherford 3) and critical limb ischemia (CLI; Rutherford 4–6) were included provided they had at least 1 lesion with > 70% diameter stenosis confirmed on live quantitative vessel angiography in a lower extremity artery. Patients with in-stent restenosis and diabetes type 1 were excluded.

Procedural characteristic and pharmacological regimen

Directional (Silver Hawk™, Medtronic), orbital (Diamondback 360°, CSI 360°) and directional with suction (Jetstream™, Boston Scientific) atherectomy (AT) devices were applied in this study. The type of AT was left to operator discretion, nonetheless directional AT was performed in soft and mixed plaques; orbital AT was applied when a lesion appeared to be calcified; and directional AT with suction was performed when thrombus was suspected. Orbital AT was always followed by the low-pressure balloon post-dilatation; and after directional AT, percutaneous transluminal angioplasty (PTA) was performed if residual stenosis was > 30%. The distal protection system was not used for any patient. Angiographic success was defined as post-procedural Thrombolysis in Myocardial Infarction (TIMI) 3 flow, no dissection or residual stenosis < 30%. If angiographic success was not achieved, bail-out stenting was performed. Acetylsalicylic acid (81 mg/day) was continued indefinitely whereas clopidogrel (75 mg/ /day) was advised to be continued for 12 months after the procedure together with atorvastatin, at the maximum tolerable dose, usually 40 mg daily.

Atherectomy devices

The Silver Hawk plaque excision system (Medtronic) is a forward cutting directional AT device. The device consists of a rotating blade inside a tubular housing with a collection space in the nose cone. The device enables the performance of AT in vessels with a diameter of 1.5–7 mm.

Diamondback 360° (CSI360°) is an orbital AT system tipped with an eccentric, diamond-coated crown. The crown rpm can vary from 60,000 to 200,000. The crown may be advanced forward and backward when it is intra-arterial. The needed diameter is achieved by increasing the speed of rotation. Faster speeds result in an increased centrifugal force, yielding a larger orbit, and this device is recommended for calcified lesions. Usually, orbital AT is performed before stenting/balloon angioplasty.

The Pathway Jetstream PV Atherectomy System (Boston Scientific) is a rotational AT device with a front-cutting tip that spins at 60–70,000 rpm. Jetstream® expandable catheters have a catheter tip that remains at a diameter of 2.1–2.4 mm when rotating clockwise and 2.4–3.4 mm when rotating counterclockwise. For below the knee interventions this device is available in a fixed size: 1.6 mm and 1.85 mm. This is the only AT device on the market with active aspiration. The derbies as well as thrombus are collected in a bag located on the console device, outside the body.

Study endpoints and definitions

Because of the observational nature of this study, no preliminary hypothesis was generated. Target lesion revascularization (TLR) was considered a primary endpoint and was defined as any symptom-driven revascularization within a previously treated segment. Unplanned amputation related to a previously treated vessel, death and a change in the Rutherford class were regarded as secondary endpoints. Furthermore, incidents of vessel perforation, dissection and distal embolization, and bailout stenting were collected.

Table 1. Demographics.

	Non-diabetic patients	Diabetic patients	P
Number	72	132	
Male	46 (63%)	88 (66%)	0.7
Age [years]	75 ± 11.3	68 ± 11.2	0.0001
Body mass index [m/kg^2]	26.5 ± 4.9	29.4 ± 4.8	< 0.0001
Coronary artery bypass grafting	10 (14%)	56 (42%)	< 0.0001
Percutaneous coronary intervention	30 (41%)	79 (60%)	0.0185
Previously revascularized peripheral artery disease	1 (5.5%)	8 (6.0%)	0.163
Arterial hypertension	71 (99%)	132 (100%)	0.9
Coronary artery disease	45 (62%)	119 (91%)	< 0.0001
Critical limb ischemia	9 (12%)	28 (21%)	0.1332
Dialysis reliant	2 (2.5%)	42 (22%)	< 0.0001
Smokers	11 (15%)	23 (17.4%)	0.8445

Safety and ethics

This retrospective study was conducted in accordance with standard ethics guidelines. Endovascular procedures were carried out by experienced interventional cardiovascular teams in a high-volume center with a vascular surgery back up within 30 min of transportation.

Owing to the observational and retrospective nature of this study, neither patient consent nor ethics committee approval was required.

Data collection and follow-up

Clinical and procedural data were collected on case report forms generated by the hospital electronic system, containing all patient hospitalization and discharge information. This system is audited for institutional quality assurance by private insurance companies and the state health fund.

Long-term follow-up data were collected during ambulatory check-ups or over the phone. The follow-up office visits were usually scheduled every 3–5 months. Some patients had phone consultations due to a lack of symptoms, and office-based follow-ups were scheduled on a further date. All outcomes of interest were confirmed using hospital discharge charts. Three patients met exclusion criteria for in-stent restenosis and 3 were lost to follow-up.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range [IQR]). Data were compared using the t-test for parametric or Mann-Whitney U-test for non-parametric continuous variables. Categorical variables are reported as frequencies (percentages) and were compared using the χ^2 or Fisher exact test, as appropriate. Survival curves were constructed using the Kaplan-Meier estimates and were compared with the log-rank test. All reported p-values are two-tailed, and $p < 0.05$ was considered as significant. GraphPad 6 Prism was used for statistical analysis.

Results

The method of diabetes control was primarily oral agents (56.3%, n = 73) followed by insulin injections (36.6%, n = 48) or a combination of both (8.3%, n = 11). Patients in the diabetic cohort were significantly younger but had considerably more risk factors including off-range body mass index, coronary artery disease, coronary artery bypass grafting, percutaneous coronary interventions and dialysis-dependent renal insufficiency (Table 1). The mean time of follow-up was 384 and 411 days in DM and nDM, respectively (p = 0.43).

Lesion characteristics were similar in DM (n = 198) and nDM (n = 106) patients with a mean number of lesions per patient equaling 1.5 in both groups. Lesion location was primarily superficial femoral artery in nDM (33%, n = 38), whereas in the DM cohort anterior tibial artery was most frequently revascularized (29.7%, n = 59). There were no significant differences in target lesions between the groups. Furthermore, there were no differences between the groups in terms of lesion morphology in the TransAtlantic Inter-Society Consensus (TASC) and the number of total chronic occlusion. There were no significant differences

Table 2. Procedural characteristics.

	Non-diabetic patients	Diabetic patients	P
Number	106	198	
Iliac	0	1 (0.5%)	1.0
Common femoral artery	1 (0.94%)	1 (0.5%)	1.0
Superficial femoral artery	38 (35.8%)	41 (20.7%)	0.064
Profunda femoral artery	0 (0%)	1 (0.05%)	1.0
Popliteal artery	9 (8.4%)	23 (11.6%)	0.09
Anterior tibial artery	20 (18.8%)	59 (29.7%)	0.265
Trunk	5 (4.9%)	13(6.5%)	0.471
Peroneal artery	10 (9.4%)	18(9%)	0.51
Dorsalis pedis	3 (2.8%)	5 (2.5%)	0.173
Calcaneal artery	3 (2.8%)	5 (2.5%)	0.173
Above the knee	49	67	
Below the knee	57	131	
Graft	1	8	0.086
Pre-procedure (% diameter stenosis)	89.7%	93.7%	0.386
Mean lesion length [mm]	76 ± 23	81 ± 19	0.148
TASC A	18 (36.7%)	24 (35.8%)	1.0
TASC B	15 (30.6%)	18 (26.9%)	0.681
TASC C	11 (22.5%)	17 (25.4%)	0.827
TASC D	5 (10.2%)	8 (11.9%)	1.00
Chronic total occlusion	20 (18.8%)	56 (28.2%)	0.073
JetStrem G2	9 (12,5%)	4 (3%)	0.0137
CSI360	20 (27,5%)	46 (34%)	0.3489
Silver Hawk	43 (50%)	82 (62%)	0.6549

TASC — TransAtlantic Inter-Society Consensus

Table 3. Periprocedural complications.

	Non-diabetic patients	Diabetic patients	P
Artery perforation	1 (1.3%)	0 (0%)	1.0
Distal embolization	0 (0%)	1 (0.7%)	1.0
Flow limiting dissection	2 (2.7%)	2 (1.4%)	1.0
Bailout stenting	2 (2.7%)	2 (1.4%)	1.0

between the groups in the choice of atherectomy, except for JetStream in favor in the case of the nDM group (Table 2).

The number of periprocedural complications was similar between the groups. The detailed periprocedural outcomes are shown in Table 3.

At follow-up there were no differences between the groups in TLR after 6 months (DM: 7.5% vs. nDM 2.8%, p = 0.224), 12 months (DM: 13.6% vs. nDM 20.8%, p = 0.232) or 24 months (DM: 15.2% vs. nDM 22.2%, p = 0.249) as shown in Figure 1. The amputation and death ratios were comparable between the groups (DM: 3% vs. nDM 1.5%, p = NS) and (DM: 2.2% vs. nDM 2.7%, p = NS), respectively, as also shown in Figure 1. In the Kaplan-Mayer analysis, there were no differences in TLR-free survival, amputation free survival and survival (p = 0.27, hazard ratio [HR] 0.714, 95% confidence interval [CI] 0.371–1.314; p = 0.81, HR 0.8, 95% CI 0.127–5.041; p = 0.557, HR 4.542, 95%

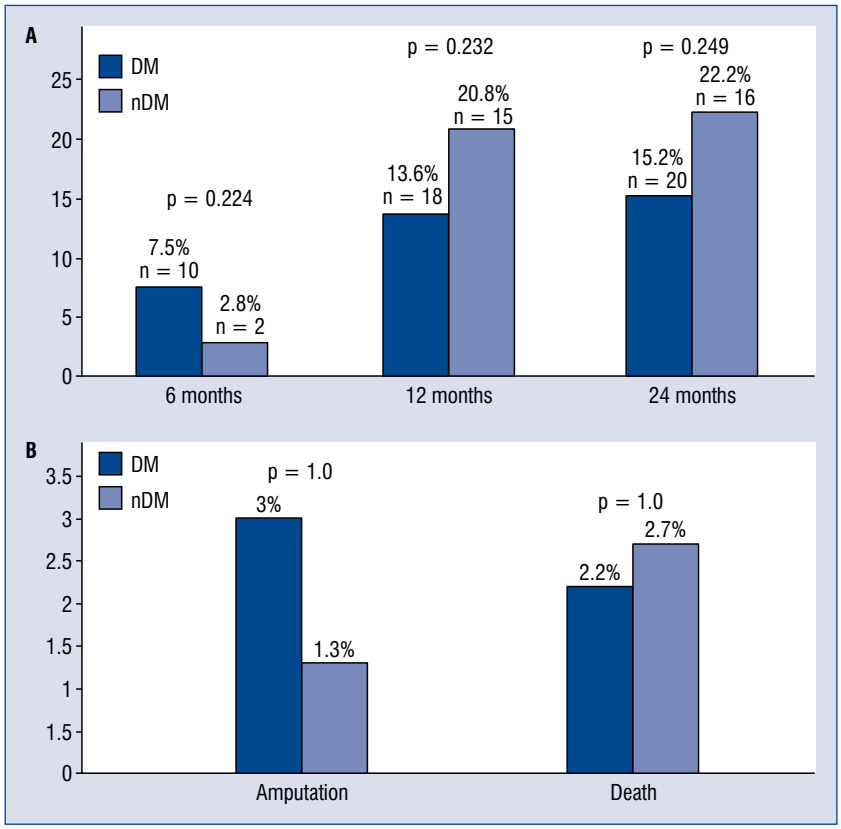

Figure 1. Target lesion revascularization (**A**), amputation and death (**B**) ratio; DM — diabetic patients; nDM — non-diabetic patients.

Cl 0.562–36.69), respectively, as shown in Figure 2. Moreover, there were no differences in the TLR between the groups depending on the artery and type of atherectomy device.

There were no significant differences in the Rutheford class between the groups during follow-up. However, there was a significant drop in the Rutherford class between groups before and after revascularization (< 0.0001) as shown in Figure 3.

Discussion

The current study presents a direct observational comparison of patients revascularized with atherectomy chosen based on plaque morphology in DM and nDM patients. According to available research, the present study, for the first-time, describes a direct comparison of long-term outcomes for different types atherectomies in diabetics vs. non-diabetics in claudicates as well as in critical limb ischemia patients. In this study, despite some discrepancies in patient baseline characteristics in favor of the nDM group, there were no differences in periprocedural complications, target lesion revascularization, amputation or death. It should be noted that the DM group consisted of high-risk patients for major cardiovascular adverse events due to numerous risk factors like end-stage renal disease, advanced coronary artery disease and obesity. Moreover, lesion characteristics are comparable between the groups. The difficulties treating PAD in diabetic patients have been driven by numerous factors including diffuse atherosclerosis causing longer lesions with smaller diameter lumen, more calcifications and greater plaque burden [10]. Furthermore, DM is associated with a more severe below-the-knee PAD, whereas risk factors, such as smoking, are associated with more proximal lesions [8].

There is very little data comparing long-term outcomes after treatment in patients with DM vs. nDM in PAD. A sub-analysis of Definitive Le comparing revascularization with SliverHawk/ /TurboHawk in diabetics and non-diabetics showed that directional atherectomy is equally effective in both groups of patients [11]. The ratio of target lesion revascularization was similar between the groups at 12-month follow-up and equaled 83.8%

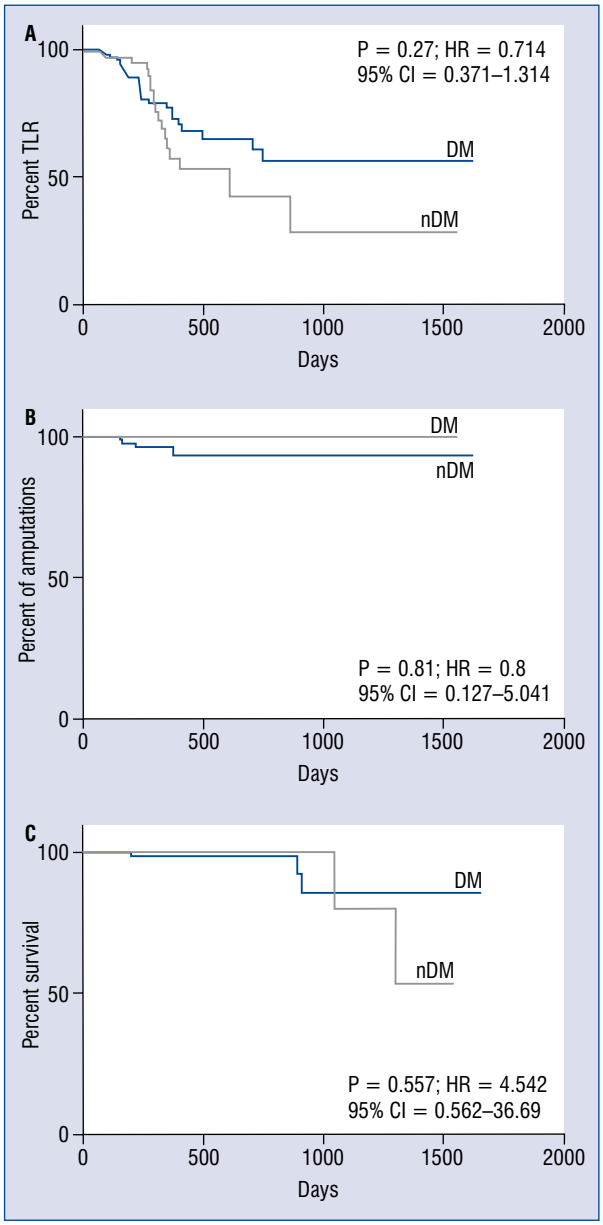

Figure 2. Kaplan-Mayer curves showing target lesion revascularization (TLR) free survival time (**A**), amputation free survival time (**B**) and survival time (**C**); DM — diabetic patients; nDM — non-diabetic patients.

and 87.5% for diabetics and non-diabetics, respectively. Just as in our database, the revascularization in Definitive Le was more frequent in case of below the knee procedures and the characteristics of demographics were similar. Nevertheless, in the Definitive Le study patients with critical limb ischemia were excluded. Lee et al. [6] compared the efficiency of plain old balloon angioplasty (POBA) in DM and nDM patients [6]. This study with a 2-year follow-up showed that POBA is less effective in diabetic patients, with a higher rate of restenosis and amputations. On the other hand, the drug eluting balloon (DEB) in the small study showed better outcomes in comparison to POBA in below-the-knee lesions at 3-month follow-up. Nevertheless, no benefits of DEB after 12 months were reported [12]. While comparing the stent technology, the Zilver PTX study reported that DM and nDM cohorts in their study had similar outcomes using the paclitaxel eluting stent [13]. Nonetheless, only superficial femoral artery was included as the target vessel. Darling et al. [7] published a direct comparison of diabetics and non-diabetics treated with POBA or bypass surgery in CLI patients. According to observations of this group, diabetics manifested an increased risk of long-term mortality, incomplete wound healing, a major amputation and restenosis, especially after POBA in comparison to non-diabetics. Furthermore, Dick et al. [14] published a study with results similar to the study mentioned earlier.

There is an interesting technology that may by combined with atherectomy in PAD and it is the local drug delivery after revascularization. Early reports on the combination of plaque modification with atherectomy and subsequent DEB seem to be promising [15, 16]. Novel technologies, including local drug delivery nano-technology, may soon become available for follow-up treatment of plaque modifications after atherectomy [17].

All patients in this study were also treated pharmacologically to reduce any major cardiovascular adverse events. Despite encouraging data on including ciliostazol in the treatment after stenting of femoropopliteal region [18], almost all the present patients were on dual antiplatelet therapy consisting of clopidogrel (75 mg) and acetylsalicylic acid (81 mg) once a day. Dual antiplatelet therapy was prescribed due to the fact that after AT, the intima-media could be exposed to blood flow, significantly increasing the risk of acute or subacute thrombosis [19].

To summarize, this study shows that the outcomes of atherectomy in PAD are similar in DM patients as compared to nDM patients. The large minimal lumen diameter obtained during atherectomy may play a crucial role in this phenomenon, which translates into a lower TLR ratio at follow-up in diabetics as well as non-diabetics.

Limitations of the study

The main drawbacks of this analysis are those inherent to any single-center, observational study [20], along with differences in baseline patient

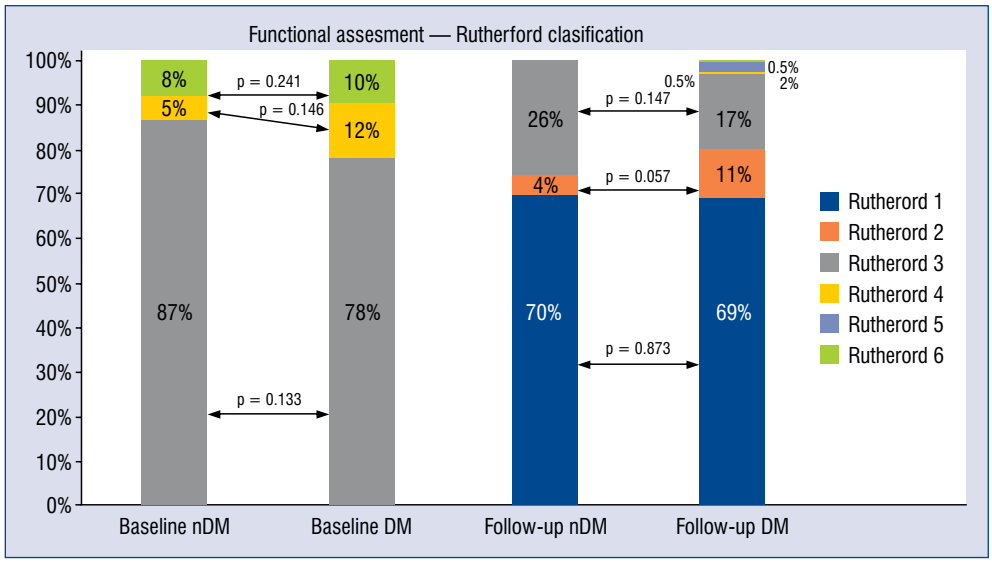

Figure 3. Rutherford classification prior and after treatment. DM — diabetic patients; nDM — non-diabetic patients.

characteristics. Nevertheless, the differences arise from the character of DM and nDM patients. The exact data on very long below the knee chronic total occlusion are unavailable. The ankle brachial index, ultrasonography with Doppler and toe pressure were not performed on each visit, making this data unsuitable for statistical analysis. This study is hypothesis-generating only.

Conclusions

In this hypothesis-generating study of patients with lower extremity PAD, plaque modifications with adjusted atherectomies appear to have similar outcomes in diabetic as well as in non-diabetic patients. Nevertheless, this should be confirmed in further controlled randomized trials.

Conflict of interest: None declared

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The Polish adaptation of the CAMbridge Pulmonary Hypertension Outcome Review (CAMPHOR)

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Abstract

Background: *Pulmonary hypertension (PH) results in severely impaired quality of life (QoL) in people with this condition. The CAMbridge Pulmonary Hypertension Outcome Review (CAMPHOR) is the only questionnaire providing a disease-specific measurement of symptoms, functioning and QoL in PH patients. It has already been adapted for use in several countries. The aim of this study was to adapt and validate CAMPHOR for the Polish-speaking population.*

Methods: *Two panels (bilingual and lay) were conducted to translate CAMPHOR into Polish. This new version was then tested by cognitive debriefing interviews with 15 patients. Finally, a postal validation survey was conducted with 56 patients on two occasions 2 weeks apart to assess its psychometric properties.*

Results: *No problems were experienced in producing a Polish translation of CAMPHOR. Interviewees responded well to the Polish CAMPHOR, finding it relevant, comprehensible and easy to complete. For all three CAMPHOR scales (Symptoms, Activity, QoL), The Cronbach alpha coefficients were above 0.8 at both time points, indicating high internal consistency. Test-retest reliability for the three scales achieved a value above 0.80. Predicted correlations with the Nottingham Health Profile provided evidence of the construct validity of CAMPHOR scales. The Polish CAMPHOR could distinguish between patients who differed according to their perceived general health and perceived disease severity. No significant differences in scores were found between participants grouped by gender or age.*

Conclusions: *The Polish version of CAMPHOR demonstrated good psychometric properties and is recommended for use in clinical practice.* (Cardiol J 2020; 27, 5: 608–615)

Key words: adaptation, CAMPHOR, quality of life, patient reported outcome, pulmonary hypertension

Introduction

Precapillary pulmonary hypertension (PH) is a condition, when mean pulmonary artery pressure increases significantly (≥ 25 mmHg) whereas the capillary wedge pressure remains within normal values (≤ 15 mmHg). It is represented in the clinical classification as group 1 — pulmonary arterial hypertension (PAH), group 3 — PH due to lung diseases and/or hypoxia, and group 4 — chronic thromboembolic PH (CTEPH). In Poland, the prevalence of PAH in adults is about 19.6 cases per million population. The number of patients increases year by year, suggesting that the disease is becoming better diagnosed [1]. A number of trials are in progress to improve life expectancy

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in this disease. However, the main problems that investigators face in planning such trials is a lack of ideal endpoints [2].

Recent clinical studies have assessed Health Related Quality of Life (HRQL) using generic patient-reported outcome measures, such as the SF-36 [3–5], EuroQol [6, 7] and Nottingham Health Profile [8]. HRQL provides information that is of interest to clinicians with a focus on symptoms and functional limitations resulting from a disease [9]. However, these measures demonstrate relatively low responsiveness, especially with PH patients [10]. For example, to obtain a minimally important difference on the SF-36 domains, scores must improve between 13 and 25 points on a scale of 0–100. A modified version of the Minnesota Living with Heart Failure Questionnaire [11, 12] has also been used [13, 14]. However, the questionnaire was not designed for patients with PH and so it cannot be concluded that changes in score are valid.

Comprehensive disease-specific measures that directly address PH characteristics are required. The CAMbridge Pulmonary Hypertension Outcome Review (CAMPHOR) is the first disease-specific questionnaire to assess both health-related QoL (symptoms and activity limitations) and QoL in patients diagnosed with PH [15]. CAMPHOR consists of three sections; symptoms (25 items), activities (15 items) and QoL (25 items). Quality of life is concerned with measuring how these symptoms and functioning affect the lives of patients, for example, whether they are able to fulfil their roles in life, communicate with others or interact socially. The measurement model, the needs-based model of QoL, argues that quality of life is the extent to which an individual is able to meet his or her basic human needs [16].

CAMPHOR is widely used in international clinical studies for evaluating the benefits patients gain from alternative treatments for the condition. It is also used to monitor the progress as well as response to treatment of individual patients in clinical practice. It is an outcome measure that shows the effects of treatment from the viewpoint of the patient. Research has shown that CAMPHOR scales are responsive to change, with effect sizes ranging from 0.31 to 0.69. It should be noted that CAMPHOR is at least as responsive as the 6-min walking test. This is often used as a primary endpoint in clinical trials, having demonstrated effect sizes that range from 0.16 to 0.34 [17].

CAMPHOR was developed in the United Kingdom (UK) and has since been adapted into 18 additional languages [18–25]. This report describes the adaptation of CAMPHOR into Polish and includes results from the translation, field-testing and psychometric evaluation of the new language version. A successful adaptation would provide a valid and reliable outcome measure for use in PH clinical practice and trials in Poland.

Methods

The process of adaptation of CAMPHOR questionnaire consisted of three main stages: translation (by means of a bilingual and lay panel), cognitive debriefing interviews with patients and a postal validation survey. Local ethics committee at Poznan University of Medical Sciences approved the study (resolution No. 728/16).

Stage 1: Translation process

The dual-panel methodology was used to translate CAMPHOR into Polish [26]. The bilingual translation panel consisted of 5 native Polish speakers (3 females and 2 males; aged from 26 to 51 years) with competence in English at the C2 level (proficient user) according to the Common European Framework of Reference for Languages (CEFR). They were asked to translate the UK English CAMPHOR into Polish, while keeping the following requirements in mind: capturing the same concepts as the original version and producing a comprehensible formulation of the concepts. Conceptual equivalence is of primary importance in this methodology. All items were discussed until an agreement was reached. A separate lay panel consisted of 5 monolingual Polish participants (4 females and 1 male; aged from 22 to 48 years). Individuals included to the lay panel were of an average to lower than average education level to ensure that the wording of the questionnaire is at an appropriate level for typical patients. Participants were presented with the translations made by the bilingual panel and asked to decide whether the phrasing and language were acceptable and sounded 'natural'. The purpose of this second panel was to ensure that the wording of items was appropriate to respondents from all educational backgrounds. The lay panel was provided with alternative formulations of items in which a consensus could not be reached by the bilingual panel participants.

Stage 2: Cognitive debriefing interviews

Cognitive debriefing interviews were conducted with PH patients from Warsaw. The patients were recruited through convenience sampling

from a single center. Eleven of the interviewees had idiopathic pulmonary arterial hypertension (IPAH), one chronic thromboembolic pulmonary hypertension (CTEPH), one had PH associated with scleroderma and two had congenital heart disease. The aim of these interviews was to check the applicability, comprehension, relevance and comprehensiveness of the translated scales with appropriate patients. The semi-structured interviews were conducted face-to-face. Respondents completed the questionnaire in the presence of an interviewer and were then asked to answer specific questions about the measure.

Stage 3: Validation

To further validate the Polish version of CAMPHOR, PH patients of mixed etiology treated in 1st Department of Cardiology, Poznan, Poland in 2016 were recruited. Pulmonary hypertension was diagnosed according to the standard criteria [27] and confirmed by right heart catherization. Detailed demographic and disease information is shown in Table 1. The CAMPHOR was administered twice by mail approximately 2 weeks apart. Patients also completed the Nottingham Health Profile questionnaire (NHP) [27] at the first administration. Demographic (sex, age, marital status, occupation) and disease information (time since diagnosis, perceived general health and disease severity) was also collected.

Statistical analyses

Non-parametric statistical tests were used throughout the analyses due to the ordinal nature of the data. Internal consistency of CAMPHOR scales was evaluated by determining the Cronbach alpha coefficients. Test-retest reliability was examined using the Spearman rank correlation coefficients. Convergent validity was assessed by comparing scores on CAMPHOR scales with those on the NHP sections.

Known-group validity is the ability to distinguish between groups of patients who differ according to some known factor. The following variables were used for this purpose: patient-perceived general health (very good/good/fair/poor) and patient-perceived disease severity (mild/moderate/quite severe/very severe). P-values < 0.05 were considered statistically significant.

Outcome measures

CAMPHOR. The CAMPHOR was originally developed and validated in the United Kingdom [15]. It consists of a 25-item symptom scale (scored 0–25), a 15-item functioning scale (scored 0–30) and a 25-item QoL scale (scored 0–25). For all scales, a low score indicates better status. All validated language versions demonstrate good internal consistency, reproducibility and validity [18–25].

Nottingham Health Profile. The NHP is a 38-item questionnaire of perceived distress that has been widely used in health research [28]. It

Table 1. Demographic and disease information of the validation sample (n = 56).

Age [years]	
Median	57.1
IQR	43.6–69.1
Gender	
Male	17 (30.4%)
Female	39 (69.6%)
Marital status	
Married/Living as married	33 (58.9%)
Divorced	5 (8.9%)
Widowed	8 (14.3%)
Single	10 (17.9%)
Work status	
Full-time	4 (7.1%)
Part-time	1 (1.8%)
Retired	21 (37.5%)
Homemaker	5 (8.9%)
Long-term sick leave	18 (32.1%)
Student	2 (3.6%)
Unemployed	5 (8.9%)
Cause of PH	
Idiopathic PAH	17 (30.4%)
Associated PAH	18 (32.1%)
Connective tissue disease	4 (7.1%)
Congenital heart disease	14 (25.0%)
CTEPH	21 (37.5%)
Patient-perceived general health	
Very good	1 (1.8%)
Good	19 (33.9%)
Fair	24 (42.9%)
Poor	12 (21.4%)
Patient-perceived disease severity	
Mild	2 (3.6%)
Moderate	11 (19.6%)
Quite severe	32 (57.1%)
Very severe	11 (19.6%)

CTEPH — chronic thromboembolic pulmonary hypertension; IQR — interquartile range; PAH — pulmonary arterial hypertension; PH — pulmonary hypertension

Table 2. Questionnaires descriptive statistics.

	N	Median	Interquartile range	Minimum–Maximum	% scoring minimum	% scoring maximum
CAMPHOR Time 1						
Symptoms	56	11	7–18	0–25	3.6	1.8
Activities	55	9	6–13	0–22	3.6	0
QoL	56	8	3–13	0–25	5.4	3.6
NHP Time 1						
Energy	53	33.3	0–100	0–100	28.6	26.8
Pain	52	12.5	0–25	0–100	42.9	1.8
Emotional reactions	53	22.2	0–44.4	0–100	33.9	3.6
Sleep	53	40	0–80	0–100	30.4	10.7
Social isolation	53	0	0–20	0–80	62.5	0
Physical mobility	51	37.5	12.5–50	0–87.5	12.5	0
CAMPHOR Time 2						
Symptoms	56	10.5	6–16	0–25	5.4	1.8
Activities	56	11.5	7–14.8	0–23	3.6	0
QoL	56	8	3–13.8	0–25	7.1	1.8

NHP — Nottingham Health Profile; QoL — quality of life

includes 6 sections, evaluating: energy level, pain, emotional reactions, sleep, social isolation and physical mobility. All sections are scored 0 to 100 with a lower score indicative of better health status.

Results

Translation

No significant difficulties were present during the translation process. In the adaptation process every additional step checks the correctness of previous stages and the results of the postal validation survey demonstrate whether the newly adapted version is reliable and valid. Therefore, no other investigations were required. Additionally, it is possible that certain words or concepts could not have been translated in a reasonable way however we did not find this to be the case. Where more than one translation was proposed by the bilingual panel, the lay panel generally reached agreement with little discussion. For example, the lay panel felt that the translation "Mam dosyć swojej choroby" expressed the feeling of being fed up more clearly than the alternative "Jestem zmęczony moją chorobą". For the item 'I feel guilty asking for help', the bilingual panel suggested three translations ("Czuję się źle/ /zawstydzony/zażenowany, prosząc o pomoc"). The lay panel considered that "zawstydzony" could be misinterpreted as meaning shyness, while the word "zażenowany" was thought to be too complicated. Therefore, the panel agreed that "źle" was the most appropriate translation for this item.

Cognitive debriefing interviews

Fifteen cognitive debriefing interviews were conducted with patients. All patients understood clearly the purpose of the interview. Most of the patients responded well to the questionnaire, they thought it was simple and easy to complete. The items were clear and comprehensible. Interviewees felt that the items reflected their situation well, that they could relate to the ideas expressed and felt that no part of their experience of PH was missing. No changes were made to the questionnaire as a result of the cognitive debriefing interviews.

Validation

Fifty-seven participants were recruited at Time 1. Of these 56 (98.2%) patients completed and returned the questionnaire at Time 2. Table 2 shows descriptive statistics for the questionnaires at both time points. High floor effects (high number of patients scoring the minimum) were observed for most NHP sections. This indicates that the NHP is not well targeted to PH patients in this sample.

Internal consistency

For all CAMPHOR scales, the Cronbach alpha coefficients were above 0.8, indicating high internal consistency (Table 3).

Table 3. Cronbach's alpha coefficients at Time 1 and Time 2.

CAMPHOR	Time 1	Time 2
Symptoms	0.94	0.92
Activities	0.89	0.91
QoL	0.94	0.94

Test-retest reliability

Test-retest reliability for the three scales was 0.81 for Symptoms, 0.89 for Activities and 0.96 for QoL. These values suggest that the measure produces low levels of measurement error.

Convergent validity

Evidence of convergent validity can be seen in Table 4 where significant correlations between scores on CAMPHOR and NHP sections at Time 1 are shown.

Association with demographic factors

Table 5 shows CAMPHOR scores for patients grouped by gender and age (below vs. above median age). No significant differences in CAMPHOR scores were found between participants grouped by gender. The Mann-Whitney U test revealed there was a significant difference found between older and younger individuals for CAMPHOR Activities and QoL scales. Older patients had significantly worse scores on these two scales compared to younger patients. The χ^2 test of independence was performed to investigate age differences in greater detail. A significant association was found between age and perceived disease severity (χ^2 (1) = 4.9, p = 0.04). Similarly, a significant relation was found between age and perceived general health (χ^2 (1) = = 7.8, p = 0.008).

Known group validity

Mann-Whitney U tests demonstrated statistically significant differences in CAMPHOR scores between patients who differed according to their perceived general health (Fig. 1) and disease severity (Fig. 2).

Patients who rated their disease severity as quite or very severe had significantly worse scores on all CAMPHOR scales than patients who rated their disease severity as mild or moderate. Respondents who

Table 4. Correlation coefficients between CAMPHOR scale scores and Nottingham Health Profile (NHP) section scores.

NHP	Symptoms	Activities	Quality of life
Energy	0.75	0.55	0.72
Pain	0.48	0.43	0.48
Emotional reactions	0.54	0.23*	0.72
Sleep	0.39	0.05*	0.45
Social isolation	0.48	0.19*	0.58
Physical mobility	0.69	0.86	0.70

Note: p = 0.01 (2-tailed) for all correlations except where marked. *Correlation is not significant at 0.05 level (2-tailed).

Table 5. Median scores by demographic factors.

	Symptoms		Activities		QoL	
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
Gender						
Male	17	10.0 (7.0–17.5)	17	10.0 (7.0–15.0)	17	8.0 (3.5–15.5)
Female	39	11.0 (6.0–19.0)	38	8.5 (5.8–12.3)	39	8.0 (3.0–11.0)
P	56	0.80	55	0.22	56	0.46
Age						
Below median	28	10.5 (3.3–17.8)	28	7.0 (5.0–10.8)	28	5.5 (2.0–10.5)
Above median	28	11.0 (7.3–19.8)	27	12.0 (8.0–15.0)	28	9.0 (5.0–15.8)
P	56	0.30	55	0.008	56	0.04

P value (2-tailed); IQR — interquartile range; QoL — quality of life

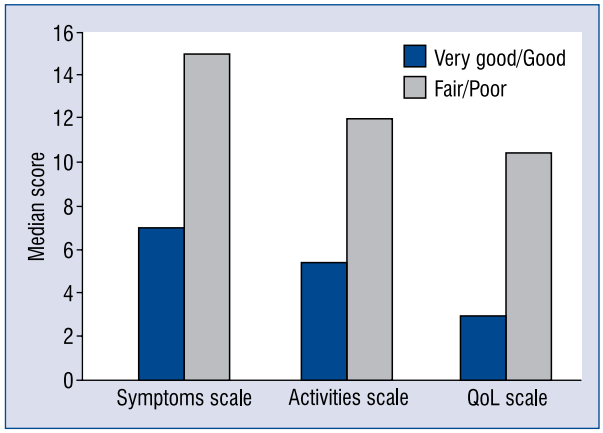

Figure 1. Median CAMPHOR scale scores by perceived general health. Note: All comparisons significant at $p < 0.01$ (2-tailed); QoL — quality of life.

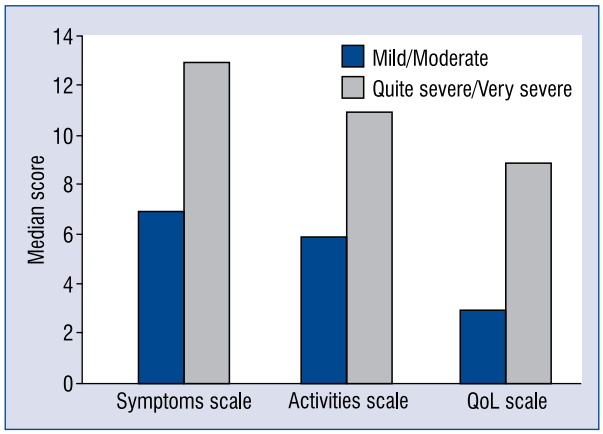

Figure 2. Median CAMPHOR scale scores by perceived disease severity. Note: Activities and quality of life (QoL) comparisons significant at $p < 0.01$ (2-tailed). Symptoms scale comparisons significant at $p < 0.05$ (2-tailed).

considered their general health to be fair or poor had significantly worse CAMPHOR scores than patients who rated their health as good or very good. This demonstrates the ability of the Polish CAMPHOR to detect meaningful differences.

Discussion

This study shows that the Polish adaptation of CAMPHOR was successful. The new language version meets the expectations of good internal consistency, test-retest reliability, and convergent and known group validity. Similar findings have been reported for previous adaptations of the CAMPHOR [18–25].

Translations that are conceptually equivalent make it possible to compare scores across countries and to combine data from different countries in international clinical trials [14]. The dual panel methodology was applied. The translation methodology used in the adaptation of CAMPHOR has been shown to produce more acceptable translations and this method is preferred in the adaptation of all need-based measures [29]. Moreover, this method places great emphasis on achieving conceptual equivalence of translated items to the original. It is important that translated items are expressed in everyday language, so that they are easily understood by future respondents, which is why the lay panel is used. In the next stage of adaptation, patients with PH in cognitive debriefing interviews confirmed the ease of answering particular items and no additional changes were necessary.. Furthermore, the use of a postal system at the validation stage was preferred, because the CAMPHOR is a patient-reported questionnaire, so adding an interviewer might have introduced response bias.

In an evaluation of internal consistency, coefficients of all three CAMPHOR scales (Symptoms, Activities and QoL) were above 0.8, indicating high internal consistency. Moreover, high test-retest coefficients obtained in all CAMPHOR scales confirmed its reproducibility. NHP was used in the validation of the original UK English CAMPHOR [15] and was adapted and validated in Polish for use as a comparator measure in the study of McKenna et al. [30]. The Polish NHP was developed using the same methodology as the Polish CAMPHOR. CAMPHOR consists of three separate sections measuring different types of outcomes: symptoms (impairment), activity limitations (disability) and QoL. The relations between scores on NHP energy section and all three CAMPHOR scales reflect the nature of the disease. Physical mobility (disability) was highly related to CAMPHOR disability and also had an overall impact on QoL scores. Overall, QoL scores were most influenced by energy level, emotional reactions and physical mobility. These results were both expected and matched findings from previous CAMPHOR adaptations [21, 23–25].

The Polish CAMPHOR scales were able to differentiate clearly between groups of patients depending on their perceived general health and perceived disease severity. The finding that older individuals reported significantly worse scores on the Activities and QoL scales was explored further. Investigation of the age differences revealed that older participants experience significantly worse in perceived disease severity and perceived general

health compared to younger individuals. This is in line with previous research that found physical functioning worsened with age in PH patients [31].

Quality of life assessment can serve as an important endpoint especially in patients with an incurable disease. It differs from HRQL in that it assesses outcomes that are of relevance and interest to patients rather than physicians [9]. Carefully developed QoL scales provide a holistic picture of the impact of disease and its treatment on the patient. In the case of chronic or terminal illness where no effective cure is available, emphasis should be placed on improving QoL as the goal of treatment [9].

The Polish CAMPHOR can be applied in both research and clinical settings in the Polish PH population. Previous research has shown that some endpoints do not indicate how patients respond to the illness [14]. This means that it is not possible to determine which interventions are of greatest value to them. Therefore, the wide range of issues covered by the CAMPHOR may support clinicians in the management and monitoring of patients.

Limitations of the study

A limitation of this study is the sample size. However, it was designed to establish the suitability of the Polish CAMPHOR rather than to describe in detail the impact of PH on patients.

Conclusions

The psychometric properties of the Polish version of CAMPHOR indicates that it is a valid and reliable measure of both HRQL and QoL in patients with PH. The new language version is recommended for use in the Polish population who speak Polish.

Acknowledgements

Researchers wishing to use the CAMPHOR questionnaire should contact Galen Research (gr@galen-research.com).

Conflict of interest: None declared

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Cardiovascular disease during the COVID-19 pandemic: Think ahead, protect hearts, reduce mortality

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Abstract

Coronavirus disease 2019 (COVID-19) is rapidly spreading globally. As of October 3, 2020, the number of confirmed cases has been nearly 34 million with more than 1 million fatalities. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is accountable for COVID-19. Newly diagnosed and worsening cardiovascular disease are common complications in COVID-19 patients, including acute cardiac injury, hypertension, arrhythmia, myocardial infarction, heart failure and sudden cardiac arrest. The mechanisms contributing to cardiac disease burden include hypoxemia, inflammatory factor storm, dysfunctional angiotensin converting enzyme 2 (ACE2), and drug-induced cardiac toxicity. Notably, the macrophages expressing ACE2 as direct host cells of SARS-CoV-2 secrete chemokine and inflammatory cytokines, as well as a decrease in cellular immune responses to SARS-CoV-2 infection due to elevated exhaustion levels and dysfunctional diversity of T cells, that may be accountable for the "hyperinflammation and cytokine storm syndrome" and subsequently acute cardiac injury and deteriorating cardiovascular disease in COVID-19 patients. However, no targeted medication or vaccines for COVID-19 are yet available. The management of cardiovascular disease in patients with COVID-19 include general supportive treatment, circulatory support, other symptomatic treatment, psychological assistance as well as online consultation. Further work should be concentrated on better understanding the pathogenesis of COVID-19 and accelerating the development of drugs and vaccines to reduce the cardiac disease burden and promote the management of COVID-19 patients, especially those with a severe disease course and cardiovascular complications. (Cardiol J 2020; 27, 5: 616–624)

Key words: COVID-19, angiotensin converting enzyme 2, cardiovascular complications, inflammatory factor storm, endotheliitis, online consultation

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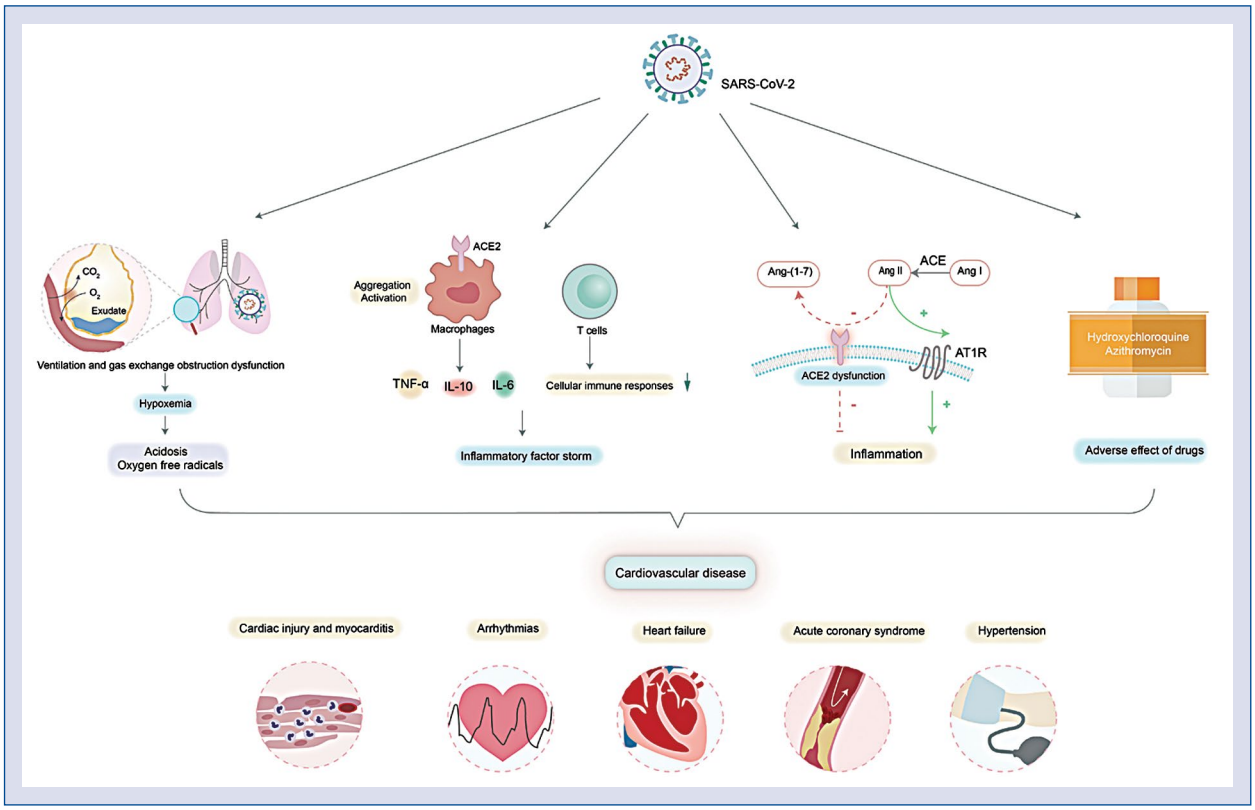

Figure 1. Coronavirus disease 2019 (COVID-19) and cardiovascular disease; SARS-CoV-2 — severe acute respiratory syndrome coronavirus 2; ACE2 — angiotensin-converting enzyme 2; Ang — angiotensin; AT1R — angiotensin II type 1 receptor; TNF-α — tumor necrosis factor alpha; IL-10 — interleukin-10; IL-6 — interleukin-6.

Introduction

Coronavirus disease 2019 (COVID-19) is rapidly spreading globally. As of October 3, 2020, the number of confirmed cases has been nearly 34 million with more than 1 million fatalities. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is accountable for COVID-19 and its sequence analysis has the smallest genetic distance from bat coronavirus and shares a 79.5% sequence identity to SARS-CoV [1]. SARS-CoV-2 has a much more efficient transmission through active pharyngeal viral shedding at the time when symptoms are still mild and typical of upper respiratory tract infection, and spreads much faster than SARS-CoV [2]. SARS-CoV-2 can infect humans by gaining S protein-driven viral entry to a cell by utilizing angiotensin converting enzyme 2 (ACE2) [3, 4].

Patients with COVID-19 have multiple organ system dysfunction [5–7], and this was further confirmed by the latest pathological findings from systematic autopsy (37 cases) and percutaneous multiple organ biopsy (54 cases) [8]. According to the largest study to date [9] and recent data from other studies [5, 6, 8, 10–12], acute cardiac injury and underlying cardiovascular disease (CVD) are common in patients with COVID-19. On the other hand, patients with cardiovascular comorbidities are more prone to suffer from COVID-19, which in turn can cause deterioration of their CVD. This work reviewed the cardiovascular complications in COVID-19 patients, the underlying mechanisms, the management, and the prospect and challenges, aiming to reduce the cardiac disease burden and promote the management of COVID-19 patients, especially those with a severe disease course and cardiovascular complications (Fig. 1).

COVID-19 and CVD

Cardiac injury and myocarditis

Abnormal elevation of cardiac injury biomarkers is widely present in patients with COVID-19 and is likely associated with infection-related myocarditis, right heart strain, and/or ischemia [10]. As for outcomes, the cardiac injury bio-markers are closely related to the disease progression and prognosis [10]. In a cohort study of patients

with COVID-19, cardiac injury occurred in 19.7% of patients during hospitalization, and it was an independent risk factor for in-hospital mortality [10]. Cardiac injury was diagnosed mainly by an increased level of high-sensitivity cardiac troponin I (hs-cTnI). Patients with cardiac injury had a higher prevalence of chronic disease, including hypertension, diabetes, coronary artery disease, cerebrovascular disease, chronic heart failure (HF), and cancer. As for clinical outcome, cases with cardiac injury had much higher fatality rates (51.2%) than those without cardiac injury (4.5%). In a retrospective and multicenter cohort study of 191 patients with COVID-19 from hospitals in Wuhan, China, acute cardiac injury was observed in 17% of all cases, 59% of non-survivors and 1.0% of survivors. Hs-cTnI were 22.2 pg/mL and 3.0 pg/mL in non-survivors and survivors, respectively. In addition, levels of hs-cTnI were elevated in non-survivors compared with survivors throughout the clinical course, and increased with illness deterioration [6]. Taken together, these findings are supportive of the idea that myocardial injury is closely related to the severity and prognosis of patients with COVID-19.

SARS-CoV-2 can cause myocarditis [13–15]. In a case report of a patient with the clinical presentation of myocarditis, the cardiac function sharply decreased and the heart size showed significant enlargement with troponin T of more than 10,000 ng/L, creatinine kinase-MB 112.9 ng/L and B-type natriuretic peptide (BNP) was up to 21,025 ng/L [15]. Notably, there is no clear evidence that SARS-CoV-2 can directly impair the myocardium and cause viral myocarditis, because neither SARS-CoV-2 in myocardial tissue nor substantial damage were detected in heart tissue obtained from postmortem biopsies [13, 16]. The most recent pathological evidence from deceased patients undergoing necropsy indicated no viral particles in cardiac parenchymal cells, which is supportive of previous findings [17]. Thus, it appears that myocarditis is likely secondary to an inflammatory storm, right heart strain and/or ischemia.

Arrhythmias in COVID-19

Electrocardiogram abnormalities and arrhythmias were observed in more than 70% of patients with SARS and are also common in patients with COVID-19 [18–21]. More than 74% of patients with COVID-19 showed electrocardiogram abnormalities and arrhythmias [22].

Sinus tachycardia is commonly observed in COVID-19 patients reporting palpitations, whereas atrial tachycardia and atrial fibrillation are common in patients with symptoms of fatigue and chest tightness. Ventricular premature beats and paroxysmal ventricular tachycardia (VT) are common in patients with palpitations, dizziness, and even syncope. In severe cases, patients suffering from an inflammatory storm are at high risk of sustained VT and even ventricular fibrillation [22]. Patients with COVID-19 who develop cardiac injury often present with sinus tachycardia [19]. Bradyarrhythmias are infrequent in patients with COVID-19, but they seem to occur suddenly and most of these cases are due to high-level atrioventricular block [22]. The QTc interval was 431 ms in patients with COVID-19 and 12.9% of cases showed prolonged QTc interval [22]. Hydroxychloroquine and azithromycin, which are used as off-label drugs to treat COVID-19 in some areas, can further enhance QT prolongation and may predispose patients with and without underlying CVDs to potentially life-threatening torsade de pointes VT [23–25].

The abnormal electrocardiogram findings were related to the underlying severity of COVID-19 patients. In a case series of COVID-19 patients with ST-segment elevation, 72% of cases died in the hospital [20]. Compared with the non-invasive care unit (ICU) group, the proportion of abnormal Q waves was higher in the ICU group (33.3% vs. 3.9%) [22]. Abnormal Q waves often indicate myocardial necrosis. Viral infection can aggravate the original myocardial disease and increase the risk of critical illness through mechanisms such as immune damage, aggravation of microvascular ischemia and induction of apoptosis.

Heart failure and sudden cardiac arrest

Heart failure is common in cases with COVID-19 [5, 26]. In a retrospective study of 112 cases with COVID-19 divided into non-survivors (17, 15.18%) and survivors (95, 84.82%), there were 27 (28.42%) and 13 (76.47%) cases with HF, respectively. The most recent report to date from Italy indicated that the second most common comorbidity in patients with COVID-19 admitted to ICUs were cardiomyopathy and HF. This finding is also supportive of the idea that HF may predispose individuals with COVID-19 to a worsening clinical outcome [5]. Even among COVID-19 patients without chronic underlying disease, those patients developing acute HF within a short time are prone to sudden cardiac arrest and the course of the disease often deteriorates rapidly [18].

Heart failure in cases with COVID-19 appears secondary to acute respiratory distress syndrome

(ARDS), acute respiratory failure, or other serious respiratory complications [18]. Pulmonary artery hypertension and pulmonary heart disease due to increased pulmonary vascular resistance leads to increased right ventricular strain and right HF. One should be alert to HF to reduce mortality. Moreover, COVID-19 patients at risk often have diastolic dysfunction and/or microvascular disease with increased left-sided filling pressures, which in case of a superinfection and fluid overload, can aggravate left-HF and increase pulmonary edema thereby deteriorating ARDS.

Acute coronary syndrome

Acute coronary syndrome (ACS) ranks second after respiratory failure as the cause of fatality [22, 26], and most cases in patients with COVID-19 are secondary to severe respiratory failure. Lactic acid accumulation and hypoxia caused by respiratory failure and hypercoagulation accelerates the occurrence of acute myocardial infarction (AMI), especially in cases with underlying CVD. Emergency percutaneous coronary intervention (PCI) should be considered to improve the ischemia--reperfusion injury. Given the lack of negative pressure cardiac catheterization chambers during the COVID-19 pandemic, particularly in regions with less advanced health-care systems, PCI as an emergency procedure has to be reconsidered, particularly for non-ST-segment elevation myocardial infarction, and prehospital emergency intravenous thrombolytic therapy is generally recommended. Expert consensus and guidelines on the management of ACS emphasizing the emerging role of intravenous thrombolytic therapy during the COVID-19 pandemic have been presented by scientific societies or groups on the front line against COVID-19 [27–29].

Hypertension

Half of cases with COVID-19 have comorbidities and the most common one is systemic arterial hypertension, which is associated with the severity of COVID-19 and in-hospital death [6, 7]. In a retrospective cohort study, 30% of cases had hypertension and the prevalence of hypertension in non-survivors (48%) was twice as much as that in non-survivors (23%) [6]. In a recent study, hypertension was the most common comorbidity (49%) in patients with laboratory-confirmed COVID-19 referred for ICU admission in the Lombardy region of Italy [5]. In a study by Huang et al. [7], 15% of cases have hypertension and the ICU group had higher systolic blood pressure as compared to the non-ICU group.

Mechanisms of CVD in COVID-19

At present, the mechanisms underlying cardiac injury and other CVDs in patients with COVID-19 are not well defined. Possible mechanisms are the following: an excessive inflammatory reaction, severe hypoxemia, dysfunctional ACE2 with upregulation of the renin–angiotensin system, cardiac toxicity due to drug-drug interactions such as azithromycin and hydrochloroquine causing acquired long QT syndrome with torsade de pointes ventricular tachycardia.

Hypoxemia

Respiratory infection leading to insufficient oxygen supply is the main cause of hypoxemia [5, 6, 17]. In the most recent work by Wang et al. [17], pathologic investigations of fatal cases undergoing necropsy provide new evidence contributing to the severe dysfunction of ventilation and gas exchange obstruction in patients with COVID-19. The gross anatomy of the lungs showed moderate bilateral pleural effusion and pleural adhesion in 2 patients and hepatization of lung tissue was observed. As for microscopic manifestation, a massive serous and fibrinoid exudate was observed in the alveolar spaces [17]. On the other hand, infection-induced increased metabolic requirements need an enhanced oxygen supply, which in turn results in severe hypoxemia. And hypoxemia, in turn, may lead to increased anaerobic fermentation and subsequently acidosis, oxygen free radicals, and ultimately cardiac injury. Among COVID-19 patients with underlying CVD the risk of hypoxemia is increased. And this hypoxemia can aggravate cardiac injury and accelerate the progression of CVD. These findings may explain the high rate of ACS, acute HF and fatal arrhythmias in severe cases. Notably, emerging pathological evidence from post mortem examination indicates pulmonary hemorrhage which may also be accountable for hypoxemia induced by suboptimal ventilation [17]. However, the causes of hypoxemia and its impact on the progression of ARDS needs to be further elucidated.

Inflammatory factor storm

Cytokine storm plays a vital role in the pathogenesis of coronavirus-caused tissue damage and entails a vast amount of cardiac injury in patients infected by coronaviruses [6, 7, 17, 30]. As for patients with COVID-19, the level of interleukin-6

(IL-6) was higher in non-survivors than in survivors throughout the clinical course, and increased with illness deterioration [6]. In Huang's study, higher levels of plasma cytokines and chemokines were higher in ICU patients than non-ICU patients [7].

The most recent evidence provides novel contributions for a better understanding of the immune responses during COVID-19 [17, 30, 31]. First, pathological evidence obtained from fatal cases due to COVID-19 indicates that a direct viral infection of the macrophages expressing ACE2 results in the extraordinary aggregation and activation of macrophages. These macrophages infected by SARS-CoV-2 secrete chemokines and inflammatory cytokines including IL-6, IL-10 and tumor necrosis factor alpha (TNFα). These findings are supportive of the idea that macrophages act as direct host cells of SARS-CoV-2 and potential drivers of "inflammatory factor storm" or "cytokine storm" in COVID-19 [17]. On the other hand, decreased cellular immune responses to SARS-CoV-2 infection were also identified. Elevated exhaustion levels and dysfunctional diversity of T cells may be another mechanism accountable for the "cytokine storm syndrome" in COVID-19 [30]. Previous studies indicated that multi-functional T cells can better control human immunodeficiency virus and are correlated with better outcomes during vaccination. However, in Zhang and colleagues' study [30], SARS-CoV-2 infection caused dysfunctional CD4+ T cells and promoted extraordinary activation and possibly subsequent exhaustion of CD8+ T cells. Moreover, severe cases infected by SARS-CoV-2 showed significantly decreased frequency of multi-functional CD4+ T cells compared with healthy controls and mild cases. These findings are supportive of the idea that compared to other coronaviruses, SARS-CoV-2 may possess a unique immunopathological mechanism which predisposes infected cases to deteriorate rapidly.

Dysfunctional ACE2

Previous data indicated that coronavirus can lead to ACE2 dysfunction and subsequently abnormal activation of renin–angiotensin system, eventually resulting in an hyperinflammatory reaction. The down-regulation of ACE2 was observed in animal models of SARS and H7N9 infection, and this can be counter regulated by angiotensin receptor blockers (ARBs) [32, 33]. As for the cardiovascular system, the decreased ACE2 expression in the myocardium was observed in animals and patients infected by SARS-CoV [34]. Infection with the human SARS-CoV in mice led to an ACE2-dependent myocardial infection with a marked decrease in ACE2 expression, which was supportive of a critical role of ACE2 in mediating SARS-CoV infection in the heart. In patients infected by SARS-CoV, the virus was also detected in autopsied human hearts and its presence was associated with marked reductions in ACE2 protein expression [34]. Though no evidence of SARS-CoV-2 directly infecting myocardium, based on the information that SARS-CoV-2 and SARS-CoV share the similar structure and function [4, 35]. We can make some rational and scientific inferences that SARS-CoV-2 may lead to cardiac injury by affecting ACE2 function. Notably, emerging evidence from post-mortem analysis are supportive of this idea [36]. In a serial section of tissues, Varga et al. [36] found evidence of direct SARS-CoV-2 infection of the endothelial cell and diffuse endothelial inflammation. The fact that endothelial cells of multiple systems expressing dysfunctional ACE2 receptor due to direct SARS-CoV-2 infection of the endothelium or immune-mediated facilitates the induction of endotheliitis and may be the main mechanism underlying multiple system organ failure, including CVD [36]. Drugs or vaccines targeting these processes may provide a therapeutic target.

Adverse effect of drugs

Given the fast spread and high transmission rates of COVID-19, there are many programs aiming at developing pharmaceutical drugs for treatment and prevention of COVID-19. While ongoing and future studies should be actively supported, caution is needed for the off-label use of previously approved drugs due to cardiac toxicity, especially in severe cases with multiple comorbidities and polypharmacy [5–7, 21]. In a small study conducted by Gautret et al. [37] attracting much attention, hydroxychloroquine treatment was significantly associated with viral load reduction/disappearance in the pharynx of COVID-19 patients. In China, hydroxychloroquine is already recommended in the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment. Other countries have followed these recommendations. However, clinical and in vitro experimental evidence has reported hydroxychloroquine-induced cardiac toxicity [21, 38]. When hydroxychloroquine was prescribed in severe cases, patients with underlying CVD are prone to hydroxychloroquine-induced cardiac toxicity and this is likely to aggravate underlying disease. In a recent study, patients with COVID-19 treated with hydroxychloroquine and azithromycin had severe QTc interval prolongation but they had

a normal QTc at baseline [21]. Another factor should also be considered, namely synergistic toxicity. Patients with COVID-19 are often concurrently prescribed a drug in combination with many other drugs.

Management of CVD during the COVID-19 pandemic

In the management of COVID-19, the treatment of patients with acute myocardial injury and underlying CVD adheres to the principles of comprehensive treatment. In addition to the general and supportive treatment, antiviral therapy is recommended in expert consensus and guidelines. However, there are no targeted antiviral agents for SARS-CoV-2. Though lopinavir/ritonavir and hydroxychloroquine showed effectiveness in some cases, recent evidences from a randomized, controlled, open-label trial published in 'New England Journal of Medicine' [39] showed that no benefit was observed with lopinavir/ritonavir treatment beyond standard care in hospitalized adult patients with severe COVID-19. As for chloroquine, the article by Raoult [40] to support the potential of the chloroquine has been retracted due to "expected standard". In addition, the same dosing regimen reported by Molina et al. [41] showed no evidence of a strong antiviral activity or clinical benefit of the combination of hydroxychloroquine and azithromycin for the treatment of the hospitalized patients with severe COVID-19. Thus, the therapeutic value and safety of these antiviral agents are still under investigation with ongoing trials.

Respiratory support

Depending on the clinical condition, supplemental oxygen and invasive respiratory support should be considered as expert consensus guidelines recommend. However, more awareness is needed when ICU capacity is overwhelmed. Viral transmission through exhaled air dispersion during respiratory support can accelerate interpersonal transmission in the airtight wards, and this situation may be worse when two or more patients are using a shared ventilator due to limited heath care resources [42].

Anti-inflammatory treatment

As for inflammatory storm, the administration of immunoglobulins can effectively ameliorate the strong immune response to SARS-CoV-2. Recent pathological evidence from post mortem examinations indicated characteristic abnormalities of the mucous plug with fibrinous exudate in the alveoli and the activation of alveolar macrophages [17]. These findings are supportive of the potential of the IL-6 receptor antagonist tocilizumab for severe and critically ill patients with COVID-19. The use of glucocorticoids is controversial and currently not recommended in the current interim guidance from the World Health Organization on clinical management of COVID-19 due to its potential inhibition of viral clearance and prolongation of the duration of viremia [43]. Both artificial liver support systems and continuous renal replacement therapy showed potential in the treatment of SARS and MERS, and are also recommended in the guidelines of the Chinese National Health Commission against COVID-19.

Drug treatment

As for those with CVD, statins, β-blockers, ACEIs/ARBs, and antiplatelet and anticoagulant agents should be actively prescribed as appropriate to protect the cardiovascular system. As for AMI, emergency PCI should be the first choice if a negative pressure catherization room is available. The strategies to treat arrhythmias in patients with COVID-19 should be according to the type of arrhythmia and the hemodynamic status of the patient.

Most notably, the use of ACEIs/ARBs in patients without CVD are not recommended. Whether ACEIs/ARBs are beneficial in COVID-19 patients without hypertension, HF, ischemic cardiomyopathy or other diseases are still under investigation.

Device treatment

Regarding cardiac pump failure, life supportive treatments such as a temporary pacemaker, left ventricular assist device, and extracorporeal membrane oxygenation (ECMO) should also be considered early in the disease course. Given that severe or critical COVID-19 cases who can be successfully weaned off ECMO have been reported to be rare, some have argued that ECMO might not be an optimal treatment strategy during the COVID-19 pandemic. Herein provided is 1 case supportive of ECMO as a life-saving procedure to provide both respiratory and cardiac support for patients suffering from cardiac and respiratory failure. This case is a patient with laboratory-confirmed COVID-19. Her condition rapidly deteriorated under conventional therapy. VV-ECMO was used to provide both respiratory and cardiac support. She had fully recovered from the condition that necessitated the use of ECMO after about 7 weeks. The ECMO treatment in this case is supportive of the use of ECMO during the COVID-19 pandemic.

Psychological assistance

The relationship of mental disorders and CVD is well known. Mental health disorders, such as anxiety, fear, depression, and insomnia are very common in patients, health professionals, and the general public [44, 45]. Governments, organizations, and institutions have implemented policies to improve these mental health challenges. Though the potential of mental health disorders to aggravate underlying CVD or induce acute cardiac injury during the COVID-19 pandemic remains unknown, psychological assistance should be provided as soon as possible by a hotline or online consultation [44–46].

Online consultation

Given that COVID-19 has overwhelmed many healthcare systems, non-infectious disease, intensivists, and cardiologist physicians have been recruited from other medical specialties, without adequate training, to play this role. During the COVID-19 pandemic in China, specialists in other cities were invited for online consultation for the management of severe and critical cases in hospitals. When COVID-19 was rapidly spreading all over the world in March of 2020, hospitals in China also shared clinical experiences with specialists in Italy and the United States. Fast and effective online consultation are important when the appropriate specialists are not available. Social distancing however does not mean social isolation. We should all stand together against the COVID-19 pandemic globally with the help of an online consultation system.

Last but importantly, thinking ahead is a precondition for protecting hearts and reducing mortality. We must bear in mind the clinical presentation and other clues of myocardial injury in this challenging disease, and carefully monitor cardiac function and myocardial injury. Based on our experience in Wuhan hospitals, the typical clinical manifestation with angina pectoris, shortness of breath and dyspnea is often paralleled with increased cardiac injury biomarkers. However, an atypical clinical presentation of cardiac injury is often blunted by the symptoms of lung infection. It should be carefully identified to take action before the condition rapidly deteriorates.

Prospect and challenges

Cardiovascular diseases in patients with COVID-19 are accountable for the poor prognosis especially in > 50-year old adults with underlying CVD. Recently emerging evidence helps explain the structural features of the SARS-CoV-2, the way it interacts with human cells and its infection ability [4, 47–49], however, why SARS-CoV-2 has a much more efficient transmission and spreads much faster than SARS-CoV though they belong to the same species is not known. As for CVDs, the exact mechanism by which SARS-CoV-2 results in dysfunction of the cardiovascular system, the relationship of SARS-CoV-2, ACE2 and ACEI/ARB remains unknown. Second, it is essential to develop targeted antiviral drugs and vaccines with strict standards using standard clinical-trial parameters. Third, there are some concerns that when SARS-CoV-2 is widely circulating, SARS-CoV-2 may result in an outbreak to overwhelm the healthcare systems. Fourth, there are many silent coronavirus spreaders who are infected by SARS-CoV-2 but show no symptoms. Less is known about their infectiousness and prognosis. Fifth, as COVID-19 is rapidly spreading across the world, enormous and scarce medical resources are allocated to combat the unprecedented pandemic. These efforts aiming to contain the circulation of SARS-CoV-2 will inevitably lead to absolute scarcity in other fields. Numerous pleas have been received from patients with underlying CVD, diabetes mellitus, and other conditions for routine clinical services such as elective PCI, ablation of cardiac arrhythmias, or cardiac rehabilitation. When most if not all of those patients take a back seat during the unpredictable COVID-19 pandemic, they will be critically affected and considered as a high-risk population of severe and critical conditions prone to SARS-CoV-2 infection. Therefore, preparedness for maximizing scarce medical resources across all patients is essential.

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REVIEW ARTICLE

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Feasibility of sacubitril/valsartan initiation early after acute decompensated heart failure

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Abstract

Despite significant diagnostic and therapeutic advances, heart failure (HF) is linked with high mortality and morbidity. Hospitalization for decompensated HF is still the most common cause of hospitalization in adults. What is more, a particularly high risk of hospitalization (even up to 50% of patients) is observed within a few months after a previous HF hospitalization. Sacubitril/valsartan, a first-in-class drug, contains a neprilysin inhibitor (sacubitril) and an angiotensin II receptor blocker (valsartan). In PARADIGM-HF trial investigators showed, that sacubitril/valsartan significantly reduced primary endpoint combined with cardiovascular death or HF hospitalization in patients with chronic, symptomatic HF (New York Heart Association class II–IV) with reduced ejection fraction (left ventricular ejection fraction [LVEF] ≤ 35–40%). Recently, results of the PIONEER-HF trial, which included HF patients with LVEF ≤ 40% who were hospitalized for acute decompensated HF were also published. The study proved that early, in-hospital, implementation of sacubitril/valsartan in these patients resulted in a substantially greater reduction of N-terminal prohormone B-type natriuretic peptide concentration and a lower rate of HF rehospitalizations with similar safety profile for enalapril. (Cardiol J 2020; 27, 5: 625–632)

Key words: sacubitril/valsartan, acute decompensated heart failure, angiotensin receptor neprilysin inhibitor, angiotensin receptor neprilysin inhibitors (ARNI)

Introduction

Management of heart failure (HF) is one of the most important challenges of modern medicine in highly developed countries [1]. An aging population, effective invasive treatment of coronary artery disease and the advancement of new pharmacological molecules which improve the prognosis of patients with cardiovascular diseases could explain the increase in HF prevalence [2, 3]. This is linked to the high costs of healthcare, which are mainly resulting from multiple hospitalizations due to worsening HF, as well as high mortality and poor quality of life (Fig. 1) [1, 3, 4].

Heart failure is a complex and progressive clinical syndrome caused by abnormalities of cardiac structure or function leading to inadequate cardiac output to fulfill metabolic demands or adequate cardiac output with increased left ventricular filling pressure [2]. There are multiple etiologies of HF, but it has been established that finally the same pathophysiological mechanisms are involved in the clinical progression of HF. The pathophysiology is based on progressive neurohormonal activation, involving two key systems: the renin–angiotensin––aldosterone system (RAAS) and the sympathetic nervous system (SNS). These mechanisms under physiological conditions are essential in the regulation of cardiovascular homeostasis in order to maintain proper cardiac function and perfusion of vital organs [5]. However, prolonged activation of these systems accelerates the progression of HF and promotes organ damage. Stimulation of the RAAS increases sodium and water retention, blood pressure, and also leads to fibrosis and remodeling of the myocardium and endothelial dysfunction with

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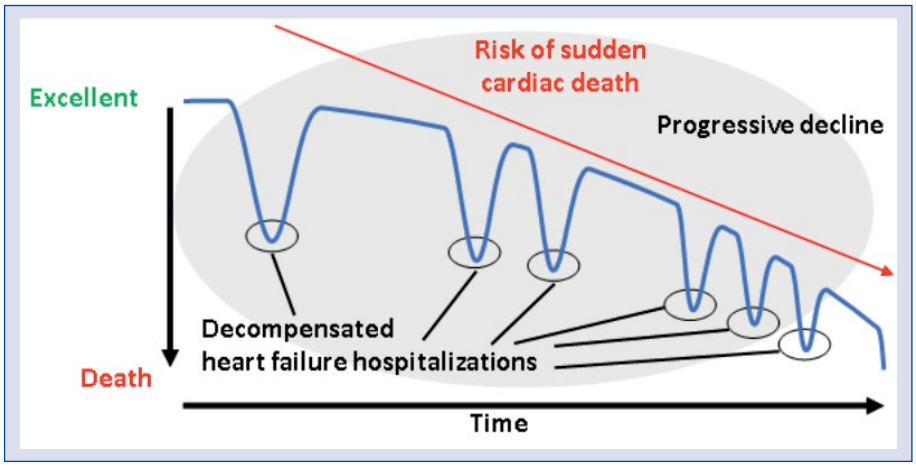

Figure 1. Clinical course of heart failure: progressive, chronic disease punctuated by acute episodes of exacerbation (based on and modified [29]).

the formation and destabilization of atherosclerotic plaques. Activation of the SNS results in vasoconstriction, increased heart rate and myocardial contractility [5].

In recent guidelines HF was classified into three subtypes — HF with reduced ejection fraction (HFrEF), HF with preserved ejection fraction (HFpEF), and HF mid-range ejection fraction (HFmrEF), according to the ejection fraction, natriuretic peptide levels and the presence of structural heart disease and diastolic dysfunction [2]. Differentiation of the HF subtype has important clinical and prognostic implications, as is a commonly accepted management with proven beneficial effects on prognosis, quality of life and acceptable safety profiles concerning patients with HFrEF [2]. However, patients with HFpEF and HFrEF have similarly high mortality risk and rate of rehospitalization after discharge [6, 7]. There are currently two interesting on-going studies on patients with HFpEF — PARAGON-HF (Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with ARB Global Outcomes in HF with preserved ejection fraction) and PARALLAX (A Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients) will investigate the benefits of sacubtril/valsartan in patients with HFpEF [8, 9].

In this review, discussion focuses on the current role of sacubitril/valsartan in the management of patients with acute decompensated HFrEF, with particular regard to results from the PIONEER-HF and other recent studies.

Current HFrEF treatment

From almost two decades treatment of chronic HF have used angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB) and beta-blockers, followed by the implementation of mineralocorticoid receptor antagonists and ivabradine into clinical practice [2]. While symptomatic management is covered mainly by diuretics [2]. An important headway in the treatment of HFrEF in recent years was the development of a new drug containing a combination of valsartan and sacubitril, belonging to the angiotensin receptor neprilysin inhibitors (ARNI) [10].

In patients with acute decompensated HF the main part of management consists of improving patient signs and symptoms, correction of volume overload, improvement of hemodynamic status and counteracting the neurohormonal hyperactivation [2, 5]. The key drugs in HF therapy in the acute setting are intravenous diuretics, vasodilators, and less commonly inotropic agents [2]. Nevertheless, despite rapid and aggressive initiation of therapy, long-term prognosis of patients with acute HF remain very poor. Therefore, there is a need for seeking for new and better therapeutic strategies to improve outcomes.

Sacubitril/valsartan

Sacubitril/valsartan is a first-in-class ARNI. This drug has a class I indication for treatment of symptomatic HFrEF in the current European and American guidelines [2, 11]. The mechanism of

action of this novel therapy includes RAAS inhibition through AT1 receptor blockade (valsartan) and neprilysin inhibiton (sacubitril), which increases levels of endogenous vasoactive peptides [12].

Besides the harmful activity of RAAS and SNS systems, other counter-regulatory pathways are activated in HF, including the natriuretic peptide (NP) system [13]. Sacubitril by inhibition of neprilysin reduces degradation of NP, bradykinin and other peptides. As a consequence, increased concentrations of mainly type A circulation (ANP) and type B natriuretic peptides (BNP) increases diuresis, natriuresis, and improves vasodilatation and relaxation of the myocardium. ANP and BNP also inhibits the secretion of renin and aldosterone. The selective blocking of the AT1 receptor reduces vasoconstriction, sodium and water retention and cardiac hypertrophy [6, 12–14].

The PARADIGM-HF trial

The PARADIGM-HF (Prospective Comparison of Angiotensin Receptor-Neprilysin Inhibitor with an Angiotensin-Converting Enzyme Inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial revealed that sacubitril/valsartan brings significant benefits among ambulatory patients with HFrEF compared with the use of RAAS inhibitor alone. Compared with enalapril, sacubitril/valsartan reduced by 20% the composite endpoint of cardiovascular death or HF hospitalization, giving a real chance for further improvement in HF therapy. Because of these results, the trial was stopped early after a median follow up of 27 months [10, 15]. In consequence, sacubitril/valsartan received a strong recommendation in the European and American guidelines as an alternative for ambulatory HFrEF patients who tolerate an ACEI or ARB and are still symptomatic [2, 11].

The PIONEER-HF trial — study design

There is limited data on sacubitril/valsartan in an acute setting, such as in patients hospitalized for acute decompensated HF and patients with severe symptomatic chronic HF. However, it seems reasonable to initiate and intensify lifesaving chronic therapy already in the hospital to decrease the risk of premature HF re-exacerbation. The goal of the PIONEER-HF (Comparison of Sacubitril/Valsartan versus Enalapril on Effect on NT-proBNP in Patients Stabilized from an Acute Heart Failure Episode) trial was to assess the safety and efficacy of sacubitril/valsartan use in hospitalized individuals with acute decompensated HFrEF [16]. Interestingly, the PIONEER-HF trial was construed early after the appearance of positive data from the PARADIGM-HF study. As a rationale for conducting this trial, the researchers highlighted that in the PARADIGM-HF approximately 40% of participants had no previous HF hospitalization, and at most 15% of patients were hospitalized for a primary diagnosis of HF during the entire study [15]. What is more, patients with actual acute decompensated HF were excluded from the PARADIGM-HF study and only less than 1% of patients had New York Heart Association (NYHA) class IV symptoms at baseline [15].

In the PIONEER-HF trial 881 patients were recruited with HFrEF (≤ 40%), currently hospitalized for acute decompensated HF with elevated NP levels (N-terminal pro–B-type natriuretic peptide [NT-proBNP] ≥ 1600 pg/mL or BNP ≥ 400 pg/mL). The randomization was not earlier than 24 h and up to 10 days from hospital admission. The patients had to be clinically stable. Inclusion and exclusion criteria from the PIONEER study are presented in Table 1. After achieving hemodynamic stabilization, the patients were randomized 1:1 to sacubitril/valsartan (n = 440) or enalapril (n = 441), and were then followed for 8 weeks. Initial dose of sacubitril/valsartan was 24/26 or 49/51 mg, and for enalapril was 2.5 or 5 mg, both given twice daily. If the conversion was made from ACEI, there was a 36-h wash-out period. The investigators aimed to up-titrate the dose of sacubitril/valsartan to 97/103 mg and enalapril to 10 mg twice daily. Finally, they selected a surrogate biomarker (NT-proBNP) as the primary endpoint. The primary efficacy outcome was a change in NT-proBNP concentration from baseline to week 4 and week 8 [16]. Secondary efficacy and safety outcomes are listed in Table 2.

Results of the PIONEER-HF trial

In the PIONEER-HF trial mean age of patients was 61 years, 72% were male and 36% were black. At randomization, the median systolic blood pressure was 118 mmHg, and NT-proBNP concentration at screening was 4812 pg/mL. The median left ventricular ejection fraction (LVEF) was 24%; two thirds of patients had NYHA class III, and approximately 10% had NYHA class IV. The median serum creatinine was 1.3 mg/dL; and serum potassium was 4.2 mmol/L. Further, approximately two thirds of patients had previously beem diagnosed with HF and 60% had at least one HF hospitalization within

Table 1. Inclusion and exclusion criteria for the PIONEER-HF trial (based on [16]).

Inclusion criteria
Adults > 18 years of age with the capacity to provide written informed consent
Currently hospitalized for acute decompensated HF with symptoms and signs of fluid overload
LVEF ≤ 40% within the past 6 months
Elevated NT-proBNP ≥ 1600 pg/mL or BNP ≥ 400 pg/mL during current hospitalization
Randomization not earlier than 24 h and up to 10 days from hospital admission
Systolic blood pressure ≥ 100 mmHg for the preceding 6 h before randomization and absence of symptomatic hypotension
No increase (intensification) in intravenous diuretic dose within the last 6 h prior to randomization
No use of intravenous vasodilators within 6 h prior to randomization
No intravenous inotropic drugs 24 h prior to randomization
Exclusion criteria
Currently taking sacubitril/valsartan or any use within the past 30 days
History of hypersensitivity, known or suspected contraindications, or intolerance to any of the study drugs, including ACEI, ARB, or sacubitril
Patients with a known history of angioedema related to previous ACEI or ARB therapy
Requirement of treatment with both ACEI and ARB
Estimated glomerular filtration rate < 30 mL/min/1.73 m^2
Serum potassium > 5.2 mEq/L
Known hepatic impairment or history of cirrhosis with evidence of portal hypertension
Acute coronary syndrome, stroke, TIA; cardiac, carotid, or other major cardiovascular surgery; percutaneous coronary intervention or carotid angioplasty, within the prior month
Implantation of cardiac resynchronization therapy within the past 3 months or intent to place
Isolated right HF due to severe pulmonary disease
Documented untreated ventricular arrhythmia with syncopal episodes within the past 3 months
Presence of hemodynamically significant mitral, aortic, or hypertrophic obstructive cardiomyopathy
History of malignancy of any organ system (other than localized and resectable skin cancers) within the past year with a life expectancy of less than 1 year
Pregnant or nursing (lactating) women

ACEI — angiotensin converting enzyme inhibitors; ARB — angiotensin receptor blockers; BNP — type B natriuretic peptides; HF — heart failure; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro–B-type natriuretic peptide; TIA — transient ischemic attack

Table 2. PIONEER-HF study end-points (based on [16]).

Primary outcome
Time-averaged proportional change in NT-proBNP concentration [time frame: baseline, week 4 and week 8]
Secondary efficacy and safety outcomes
Key safety outcomes
Number of patients with incidences of:
• symptomatic hypotension
• worsening renal function
• hyperkalemia
• angioedema
Secondary biomarkers outcomes
Change from baseline in:
• high sensitivity troponin T concentration
• BNP concentration
• ratio of BNP to NT-proBNP
Clinical outcomes:
Time to first occurrence of composite of
I. Death
II. Hospitalization for worsening HF
III. Left ventricular assist device implantation
IV. Listed for cardiac transplantation
V. Unplanned visit for acute HF requiring intravenous diuretics
VI. Increase in diuretic dose > 50%
VII. Use of an additional drug for HF

BNP — B-type natriuretic peptide; HF — heart failure; NT-proBNP — N-terminal pro–B-type natriuretic peptide

the previous year. At the time of randomization 61.7% of the patients had peripheral edema, 32.9% had rales on lungs auscultation and 93.0% received intravenous furosemide during the index hospitalization before randomization. Fifty-two percent of the patients were not receiving an ACEI or ARB at the time of hospital admission [16].

In the PIONEER-HF treatment with sacubitril/valsartan was associated with a greater time-averaged reduction in NT-proBNP concentration (primary efficacy outcome) compared to enalapril. The investigators also noted a 25.3% and 46.7% reduction in NT-proBNP concentration in enalapril and sacubitril/valsartan groups, respectively. This reduction was observed within the first week after drug initiation [16]. NT-proBNP is a biomarker of neurohormonal activation and hemodynamic stress, which plays an important role as a tool for

HF diagnosis, monitoring of therapy and prognosis. It is worth noting, that HFrEF patients with concomitant atrial fibrillation (AF) have higher concentration of NT-proBNP. However, Kristensen et al. [17] showed that NT-proBNP > 400 pg/mL in those patients had a similar value in the prediction of cardiovascular outcomes comparing to HF patients without AF [17, 18].

The PIONEER-HF study also observed a reduction in high-sensitive troponin T concentration in the sacubitril/valsartan group ($p < 0.05$). Elevation of troponin is a very frequent finding in patients hospitalized for acute decompensated HF and is associated with poor outcomes during hospitalization and increased risk of death or rehospitalizations after discharge [19]. Nakou et al. [20] already showed that troponin I concentrations may be an independent predictive marker of a sacubitril/valsartan positive response in HFrEF.

Importantly, the PIONEER-HF study also showed a 44% reduction in HF rehospitalizations and 46% reduction in a composite outcome of serious clinical events (death, HF rehospitalization, need for a left ventricular assist device, or heart transplant). What is more, previously, Desai et al. [21] showed that patients treated with sacubitril/valsartan comparing to enalapril in the PARADIGM-HF study had less frequent 30-day readmissions for any cause after HF hospitalization. The results of these studies encourages early use of sacubitril/valsartan and gives an opportunity for additional improvement of outcomes of HF patients compared to enalapril. The results of the clinical and safety outcomes of the PIONEER-HF study are presented in Tables 3 and 4.

In the PIONEER-HF study, patients hospitalized for acute coronary syndrome with concomitant signs of HF were excluded from the study. However, an on-going PARADISE-MI (Prospective ARNI vs. ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI) study enrolls patients with LVEF < 40%, and signs of HF in the post-acute myocardial infarction phase (without prior chronic HF). The PARADISE-MI study was designed to evaluate benefits of sacubitril/valsartan versus ramipril in reducing the occurrence of composite endpoint of cardiovascular death, HF hospitalization and outpatient HF occurrence in patients with new-onset HF after recent myocardial infarction [22].

There are also other studies evaluating the process of initiation and uptitration of sacubitril/valsartan following hospitalization for acute decompensated HF. The rationale of the TRANSITION (The Comparison of Pre- and Post-discharge Initiation of LCZ696 Therapy in HFrEF Patients After an Acute Decompensation Event) study was to evaluate efficacy and safety of in-hospital initiation of sacubitril/valsartan in HFrEF patients hospitalized for acute decompensated HF after clinical stabilization [23]. According to the protocol, patients were randomized within ≥ 24 h after hemodynamic stabilization (in a pre-discharge arm) or up to 14 days after discharge (a post-discharge arm). The study enrolled patients with deterioration of chronic HF or with de novo acute decompensated HF, as well as patients with or without previous ACEI/ARB therapy [24]. The primary results of the TRANSITION study demonstrated that uptitration of sacubitril/valsartan to a target dose 200 mg (sacubitril 97 mg and valsartan 103 mg twice daily) was achieved in about 45% of patients who started taking the drug before discharge, compared with 50% of patients who started the drug after discharge. The difference was not statistically significant. Adverse events prompting discontinuations of sacubitril/valsartan therapy were rare, and occurred similarly in both arms of the trial [24].

The PARADIGM-HF study recruited patients who were pre-exposed to optimal doses of enalapril (10 mg twice daily) and were then transitioned to sacubitril/valsartan (first 100 mg (sacubitril 49 mg and valsartan 51 mg), twice daily, and then sacubitril/valsartan 200 mg (sacubitril 97 mg and valsartan 103 mg), twice daily, over a 6–8 week period before randomization. In comparison, the TITRATION (Safety and Tolerability of Initiating LCZ696 in Heart Failure Patients) study was addressed to evaluate the tolerability of initiation/faster uptitration (condensed shorter 3-week and conservative 6-week uptitration) of sacubitril/valsartan in HF patients with LVEF ≤ 35%. The study population was comprised of 498 in- and outpatients, both patients pre-exposed to varying doses of an ACEI/ARB and ACEI/ARB-naive. Initially, patients were taking 50 mg sacubitril/valsartan twice a day for 5 days. The authors showed that sacubitril/valsartan was characterized by a good safety profile and tolerance regardless of time to reach the target dose. There were no statistically significant differences in the occurrence of hypotension, renal dysfunction, hyperkalemia and angioedema between 'condensed' vs. 'conservative' regimens. The secondary tolerability outcome was related to the number of patients who managed to reach the target dose 97/103 mg twice daily and to maintain it for 12 weeks. Such therapeutic success was achieved in 75.9% of the study participants

Table 3. Clinical and biomarker outcomes in the PIONEER-HF trial (based on [16]).

Clinical outcomes	Sacubitril/ /valsartan (n = 440)	Enalapril (n = 441)	Hazard ratio (95% CI)
Composite of clinical events	249 (56.6%)	264 (59.9%)	0.93 (0.78–1.10)
Death	10 (2.3%)	15 (3.4%)	0.66 (0.30–1.48)
Rehospitalization for HF	35 (8.0%)	61 (13.8%)	0.56 (0.37–0.84)
Implantation of left ventricular assist device	1 (0.2%)	1 (0.2%)	0.99 (0.06–15.97)
Inclusion on the list for heart transplantation	0 (0%)	0 (0%)	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5%)	2 (0.5%)	1.00 (0.14–7.07)
Use of additional drug for HF	78 (17.7%)	84 (19.0%)	0.92 (0.67–1.25)
Increase in dose of diuretics of > 50%	218 (49.5%)	222 (50.3%)	0.98 (0.81–1.18)
Composite of serious clinical events (death, rehospitalization for HF, implantation of a left ventricular device, inclusion on the list of patients eligible for heart transplantation)	41 (9.3%)	74 (16.8%)	0.54 (0.37–0.79)
Secondary biomarker outcomes			**Ratio of change (95% CI)**
Change in high-sensitivity troponin T concentration	–36.6 (–40.8 to –32.0)	–25.2 (–30.2 to –19.9)	0.85 (0.77–0.94)
Change in BNP concentration	–28.7 (–35.5 to –21.3)	–33.1 (–39.5 to –25.9)	1.07 (0.92–1.23)
Change in ratio of BNP to NT-proBNP	35.2 (28.8 to 42.0)	–8.3 (–3.6 to –12.7)	1.48 (1.38–1.58)

BNP — B-type natriuretic peptide; CI — confidence interval; HF — heart failure; NA — not available, NT-proBNP — N-terminal pro–B-type natriuretic peptide

Table 4. Safety outcomes in the PIONEER-HF trial (based on [16]).

Safety outcome	Sacubitril/valsartan (n = 440)	Enalapril (n = 441)	Relative risk (95% CI)
Worsening renal function*	60 (13.6%)	65 (14.7%)	0.93 (0.67–1.28)
Hyperkalemia	51 (11.6%)	41 (9.3%)	1.25 (0.84–1.84)
Symptomatic hypotension	66 (15.0%)	56 (12.7%)	1.18 (0.85–1.64)
Angioedema	1 (0.2%)	6 (1.4%)	0.17 (0.02–1.38)

*Worsening renal function was defined by an increase in the serum creatinine concentration of 0.5 mg per deciliter or more (≥ 44 μmol/L) and a decrease in the estimated glomerular filtration rate of 25% or more; CI — confidence interval

(in 78% of people in the 3-week group and 84% in the 6-week group, p = 0.07). It may be concluded, based on the results of the TITRATION study that initiation/uptitration of sacubitril/valsartan from 50 to 200 mg twice daily had a good tolerability over the 3- and 6-week process, but more gradual uptitration may have fewer side effects and may be better tolerated in patients previously treated with low doses of ACEI or ARB (or ACEI/ARB naive) [25].

What is highly important in terms of drug initiation in the acute setting, was that the PIONEER--HF trial sacubitril/valsartan was well tolerated and showed a good safety profile. Rates of the key safety outcomes including symptomatic hypotension, worsening renal function, hyperkalemia, or angioedema were comparable between the two study arms (for all p-value > 0.05). In addition, all 6 cases of angioedema in the enalapril group occurred in black patients, while the only case in the sacubitril/valsartan group was in a white patient. Trial medication was discontinued in approximately 20% of patients in both groups [16]. In contrast, in the PARADIGM-HF study, hypotension was more frequent in the sacubitril/valsartan group, while hyperkalemia, higher serum creatinine level, need for discontinuation of the study drug because of renal impairment and cough were more common in the enalapril group (for all p-value > 0.05). Sacubitril/ /valsartan was discontinued in 17.8% and enalapril in 19.8% of patients (p = 0.02) [15].

Luo et al. [26] assumed that implementation of the novel therapy with ARNI into the clinical practice is slow and they were seeking characteristics of early adopters and factors associated with ARNI prescription among patients discharged after acute HF hospitalization. They analyzed 16674 HFrEF patients hospitalized in 210 hospitals from October 2015 to December 2016. ARNI was prescribed at discharge for 6.1% of them. They showed that for-profit hospitals located in the Northern United States had significantly higher odds of ARNI prescription compared with not-for-profit hospitals located in the Western United States ($p = 0.04$ and $p = 0.02$, respectively) [26]. Further studies assessing sacubitril/valsartan will perhaps translate into a better understanding of the new evidence-based therapy and minimize differences across hospitals.

New evidence regarding the use of sacubitril/valsartan in patients hospitalized for new-onset HF or decompensated chronic HF sacubitril/valsartan was included in the European Society of Cardiology 2019 experts' clinical practice update on HF [27]. According to this new document sacubitril/valsartan, rather than an ACEI or an ARB, may be considered in these patients to reduce short-term risk of adverse outcomes. The direct introduction of sacubitril/valsartan, without the need of overtaking ACEI titration, significantly facilitates management of HF patients.

Authors of the PIONEER-HF trail pointed out some limitations of the study. They concluded that there was a need to wait for hemodynamic stability and a 36-h wash-out period in the sacubitril/valsartan group, with 6 h of obligatory observation, may require prolonged hospital stays. However, the median duration of the index hospitalization (5.2 days) was shorter than was shown in a previous analysis from the registry of European Society of Cardiology (median hospital stay was 7 days) [28]. Additionally, there was high discontinuation rate of study drug in both arms and 15% had missing data for the primary endpoint [16].

Conclusions

The results of the presented studies encourage the early initiation of sacubitril/valsartan treatment immediately after achieving clinical stabilization to improve outcomes of HF patients after hospitalization for worsening HF. Treatment of clinically stabilized HFrEF patients hospitalized for acute decompensated HF with sacubitril/valsartan significantly reduces NT-proBNP concentrations and the risk of serious clinical events. An early start of treatment with sacubitril/valsartan has a good safety profile and is not associated with an increased risk of symptomatic hypotension, renal dysfunction, hyperkalemia, or episode of angioedema compared to enalapril.

Conflict of interest: Agata Tymińska, Krzysztof Ozierański, Marcin Grabowski, Grzegorz Opolski, Paweł Balsam: fees for lectures or participation in clinical trials: Novartis, Boehringer Ingelheim.

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RESEARCH LETTER

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Impact of a nationwide COVID-19 lockdown on acute coronary syndrome referrals

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Editorial p. 478

Since December 2019, the emergence of coronavirus disease 2019 (COVID-19) in Wuhan, China, has evolved towards a global pandemic stressing healthcare providers and local authorities all over the world [1]. While national coronavirus lockdowns have led to a deferral of elective procedures, the European Society of Cardiology (ESC), has issued guidance for the diagnosis and management of cardiovascular diseases during the COVID-19 pandemic, in particular acute coronary syndromes (ACS). However, reports recently published suggest a decline in primary percutaneous coronary intervention (PCI) volumes during the COVID-19 pandemic [2, 3]. In addition to these observations, we report the immediate impact of a nationwide lockdown during the COVID-19 outbreak on ACS referrals in a tertiary care center as well as data on death tolls in Switzerland during the observation period.

Acute coronary syndrome patients and out of hospital cardiac arrests (OHCA) referred to the catheterization laboratories at the University Heart Center Zurich during the period 02/17-04/12/2020 were included. The number of ACS referrals reported 4 weeks before and after implementation of a nationwide lockdown on March 16th 2020 was compared to the same period of time in 2019.

Four weeks after March 16th 2020 ACS referrals decreased by 42% (non-ST-segment elevation myocardial infarction: –49%, ST-segment elevation myocardial infarction: –56%, unstable angina: +37%) while OHCA referrals declined by 57% (Fig. 1A). An initial decrease in ACS referrals was observed following the first report of a COVID-19 case in Switzerland on February 25th (–2 weeks) and was precipitated by the implementation of a nationwide lockdown on March 16th (Fig. 1C). Numbers of ACS and OHCA referrals remained stable for the same observation period in 2019 (Fig. 1B, D). The decline in ACS referrals observed from March 16th 2020 on was paralleled by an increase in weekly reported deaths in the population of persons aged 65 and over in Switzerland (Fig. 1E) while death numbers remained unchanged in 2019. Exposure to air pollutants is associated with an increased risk of near-term myocardial infarctions [4]. To assess the effect of restrictive actions following implementation of a lockdown on urban air quality, the time evolution of atmospheric pollutants recorded at a traffic air quality monitoring station were analyzed. Temperature monitoring revealed a significant increase in local temperature following the lockdown in 2020 (+2.2°, $p = 0.02$, Fig. 2A). As compared to 2019 an overall reduction in nitric oxides, pollutants mainly related to traffic emissions (Fig. 2B) could be observed during the COVID-19 pandemic. However, no significant difference in nitric oxides levels was observed before or after March 16th. On the other hand, an increase in atmospheric particulates (PM10, Fig. 2C) was be registered for both years following March 16th which is most probably related to the prevailing secondary origin of fine aerosols as well as seasonal Sahara dust contributions.

The present study supports previous observations and demonstrates a dramatic drop in ACS referrals within a few weeks during the COVID-19 pandemic in a tertiary care center in Switzerland which was precipitated by the implementation of a nationwide lockdown. Despite the potential

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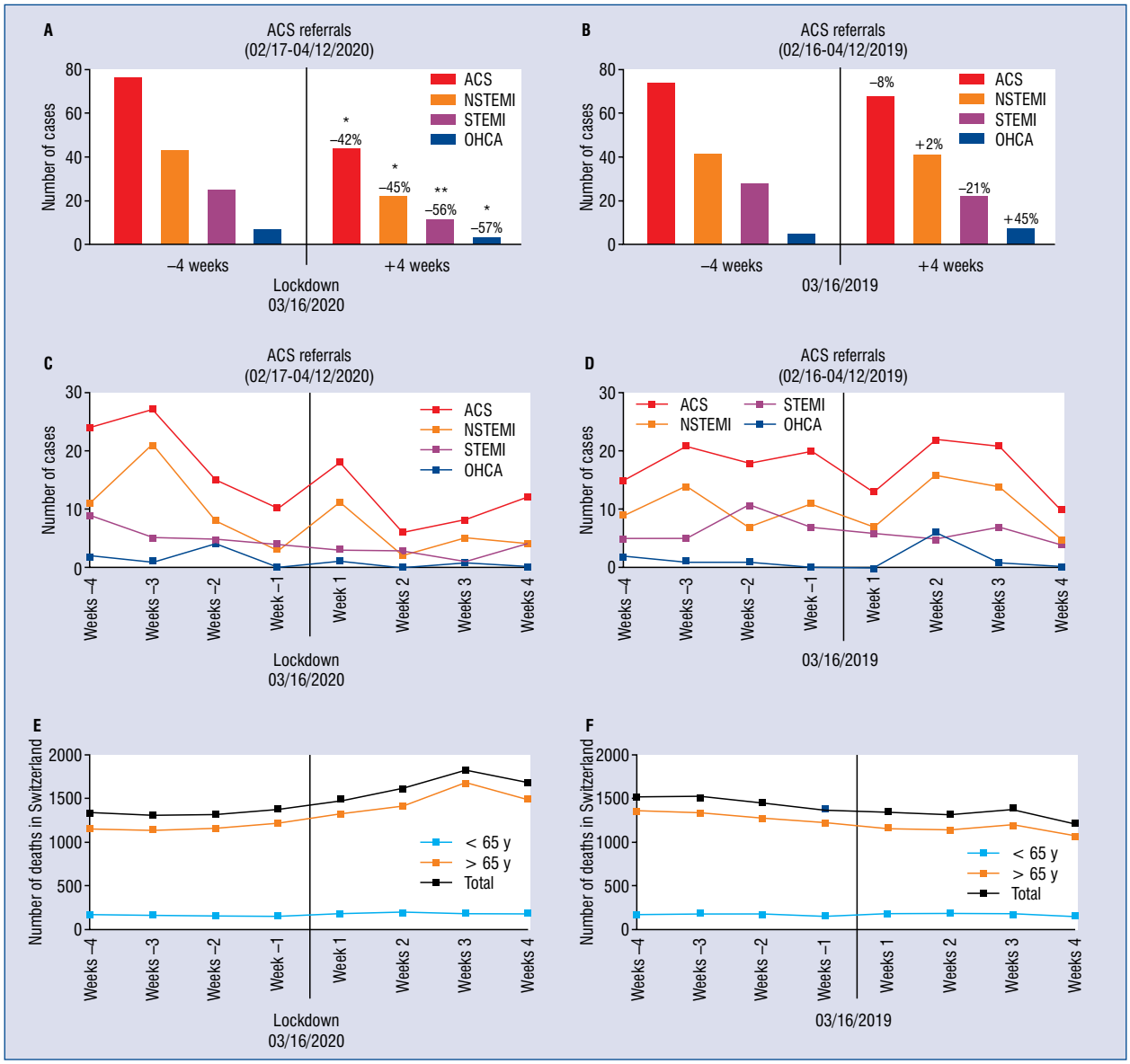

Figure 1. Acute coronary syndrome (ACS) referrals 4 weeks before and after March 16th 2020 (**A**) and 2019 (**B**). Weekly evolution of ACS referrals for the same period of time 2020 (**C**) and 2019 (**D**); *p = 0.02 and **p < 0.01 for +4 weeks versus –4 weeks. Report of death cases in Switzerland according to the Federal Office of Public Health (published 04/21/2020) for the study period 2020 (**E**) and 2019 (**F**); NSTEMI — non-ST-segment elevation myocardial infarction; STEMI — ST-segment elevation myocardial infarction; OHCA — out of hospital cardiac arrest; y — years.

beneficial effects observed on traffic related air pollution, environmental changes do not seem to explain the extent of this decline in ACS referrals. The latter is paralleled by a nationwide increase in deaths observed during the pandemic in the population aged 65 and over as compared to the same period in 2019. Considering the growing evidence suggesting a strong contribution of cardiovascular mechanisms in COVID-19 associated complications, the same concerns are shared by our colleagues regarding the fear of on an increase in overall mortality due to a high rate of untreated ACS during the pandemic [5, 6]. While administrations and healthcare systems need to continue to consider all measures necessary to contain outbreaks, campaigns in order to avoid taking a toll on other medical urgencies beyond immediate infections, in particular ACS are mandatory.

Conflict of interest: None declared

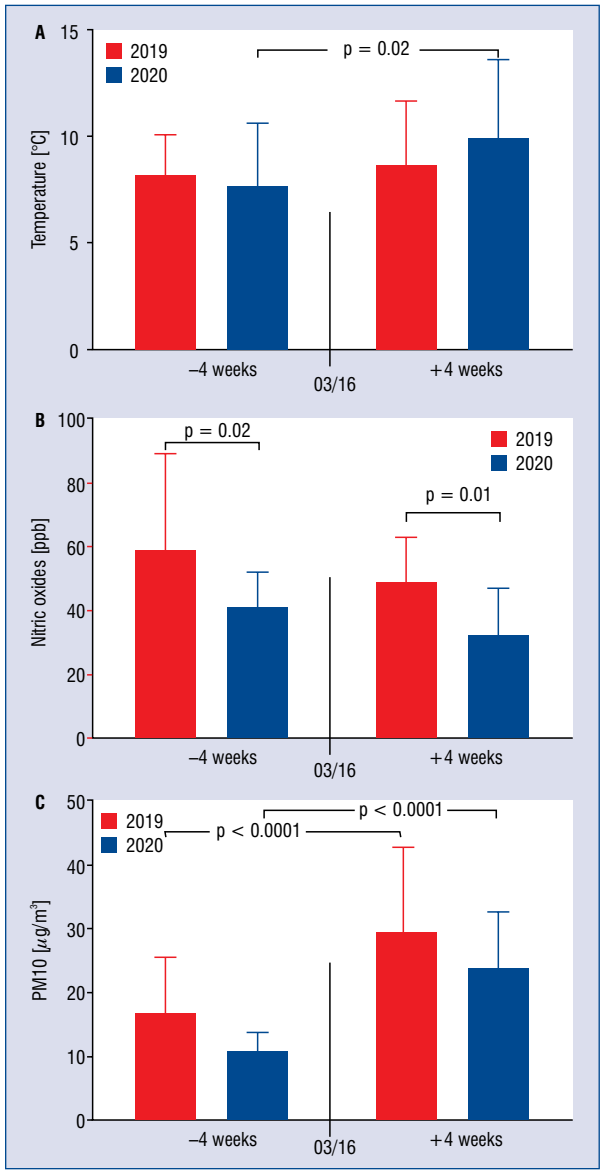

Figure 2. Analysis of temperature (**A**), nictric oxides (**B**) and particulates (PM10; **C**) variations at the traffic air quality monitoring station Rosengartenstrasse, Zurich, Switzerland. Data provided by the Office of the Environment (www.ostluft.ch). Statistical analysis was performed using two-way ANOVA (GraphPad Prism 6.0). Bars display mean values and standard deviations.

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Telephone based survey in adults with congenital heart disease during COVID-19 pandemic

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The coronavirus disease 2019 (COVID-19) pandemic is a rapidly evolving situation. Patient populations at higher risk include older adults, patients with lung disease, heart disease, and diabetes. Currently, general recommendations for adults living with congenital heart disease (CHD) appear no different from recommendations for the general population. The high-risk CHD population included patients with single ventricles or those palliated with Fontan circulation, chronic cyanosis, heart failure (HF) or cardiomyopathy, pulmonary hypertension, and significant co-existing conditions, as well as heart transplant recipients and patients with reduced immunity. This classification though, is based on expert opinions [1]. Both healthcare professionals and the CHD population have been affected by the pandemic. The lack of data and difficulty in the assessment of healthcare services are main reasons for patient anxiety.

The aim herein, was to record the impact of COVID-19 pandemic on adult CHD (ACHD) patients with and without HF, their adaptation in the current situation, their compliance to social distancing and quarantine measures and the differences between patients with HF and those without.

All regular outpatient clinics had been suspended since 11 March 2020 in Greece. The documented tertiary hospital ACHD clinic had already established a telephone-based follow-up system for all patients. In this context, 336 consecutive ACHD patients were contacted, (152 male, mean age 38.8 ± 15.3 years), between 30 March 2020 and 8 April 2020 to inform them about the service during the pandemic. They were asked about their health status, informed about how they could get their regular prescriptions without a hospital visit, explained the healthcare services which were available in case of an emergency and the availability of medical advice. They were also asked for consent to answering a questionnaire addressing the impact of COVID-19 on their mood, daily life and compliance with quarantine measures.

Of the 336 ACHD patients contacted, 146 (43.5%) had simple CHD, 138 (41.1%) had moderate complex CHD, while 52 (15.5%) had complex CHD. The diagnoses are displayed in Figure 1. Sixty-one patients (18.2%) did not answer one or more questions.

The majority of patients (78.2%) had not talked to a physician before the call.

Most patients (227, 82.5%) were self-isolated and were not working or were working from home. The impact of the COVID-19 pandemic on their mood, defined as long lasting emotional state, was severe in 18.9% and moderate in 51.6%, while 26.5% declared that there were not impaired by the COVID-19 pandemic.

One hundred thirty-three (39; 6%) patients had HF as defined by signs/symptoms or HF medication documented in patient records; mean age was 44.7 ± 16.2 years, and 66 (49.6%) were male. Patients with HF were older ($p = 0.012$) and had more complex CHD ($p < 0.001$). Significantly more ACHD patients with HF were totally self-isolated without going out at all, compared to those without HF (52.6% vs. 34.5%, $p = 0.001$). More non-HF

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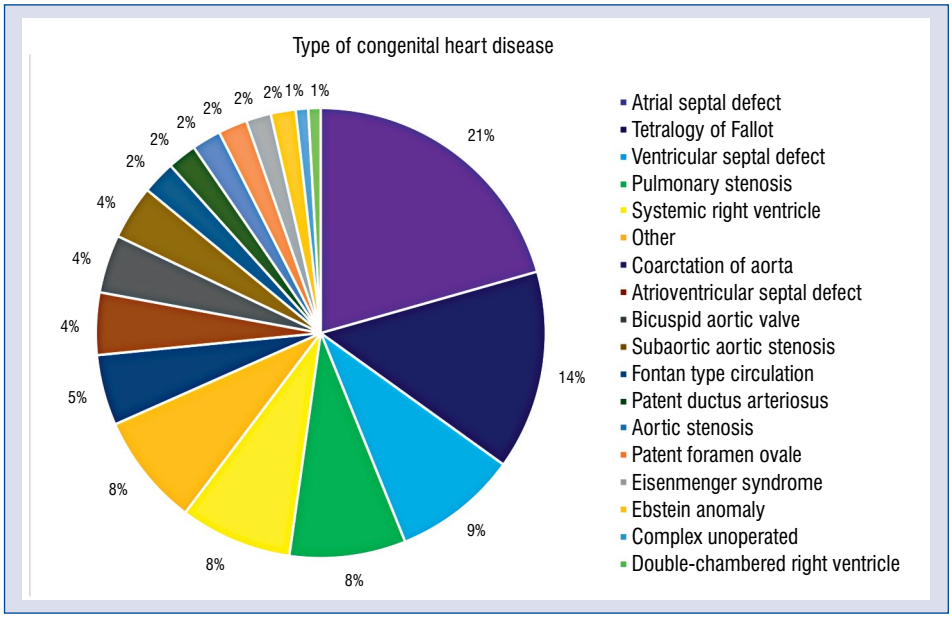

Figure 1. Congenital heart disease diagnoses.

patients stated that obligatory stay at home was the factor that impaired their mood the most (28.6% vs. 16.5% p = 0.011) compared to HF patients.

Most patients (60.8%) were concerned for their health during the COVID-19 pandemic.

Getting infected with the COVID-19 was the main fear for ACHD patients with HF (50.4% vs. 38.4%, p = 0.031) while for non-HF CHD patients main concern the was unavailability of health services (37.9% vs. 24.1%, p = 0.008).

No confirmed COVID-19 cases or COVID-19 -related events occurred up to 4 weeks after being contacted.

The COVID-19 pandemic has presented a major unanticipated burden on the workforce, organizational structure, systems of care, and critical resource supply [2].

Isolation and quarantine can precipitate depression and anxiety. Many of these consequences of the pandemic will have to be addressed by psychiatrists and mental health professionals in the months to come [3].

For chronic cardiac patients i.e. ACHD, quarantine places an additional concern on how their routine follow-up is going to be impaired and how they can access health services. This can contribute to impaired mood, and potential depression. Anxiety might arise from fear of contagion and inadequate clarity about social distancing guidelines, often made worse by less reliable media sources heightening the confusion [4].

Establishing a way of communication without physical presence that enables the patients to have access to health services and reliable information on their health status and current situation enhances their security and trust, while medical issues can be safely addressed [5]. In light of all of the above, clear instructions to the high risk ACHD population were given. In this cohort, during the first few weeks of the pandemic in Greece, there were no confirmed COVID-19 infections or urgent hospital admissions.

Most patients observed restriction measures. HF patients self-isolated completely, which is more than ACHD patients without HF. The pandemic had an impact in the mood of the majority of patients with the effect being more prominent in HF patients and obligatory isolation being more disturbing for non-HF patients compared to HF patients. This may imply that asymptomatic, younger patients were more affected socially by the pandemic, while HF patients were more concerned for their health and more typically adhered to restrictions and medical treatment. Most of our ACHD patients were concerned for their health but HF patients were more afraid of getting infected with COVID-19, while non-HF patients were concerned about the availability of health services during the pandemic.

The majority of patients observed prevention measures and followed their health status carefully. As a result, there were no COVID-19 infections or urgent admissions reported in the

present cohort during the first few weeks of lockdown in Greece. It should be stressed that this survey took place relatively early after lockdown and does not reflect the long-term consequences of lockdown in this cohort.

In conclusion, in a large cohort of ACHD in Greece, with access to remote follow-up, most patients were aware of the prevention measures for COVID-19 infection.

No confirmed COVID-19 cases or urgent admissions for cardiac reasons were documented. Patients were largely compliant with quarantine and social distancing measures. Majority reported affected mood. CHD patients with HF were older, more afraid of getting infected with COVID-19 but were rather confident of healthcare services.

Telecommunication was useful in establishing essential contact with ACHD patients.

Conflict of interest: None declared

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RESEARCH LETTER

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First experience with sodium-glucose co-transporter 2 inhibitors in Polish patients with cardiovascular diseases

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Type 2 diabetes mellitus (DM2) is a serious public health burden, and is one of the prime causes of morbidity and mortality in patients with cardiovascular diseases (CVD), like coronary artery disease (CAD), heart failure (HF), stroke or peripheral artery disease [1–4]. However, until recently, DM2 management with tight glycemic control, has not been associated with any major improvement in terms of survival in patients with CVD. Thus, the recent introduction of a novel class of agents for the treatment of DM2 — sodium-glucose co-transporter 2 inhibitors (SGLT2i) — has proven to be a breakthrough. These inhibitors combine proximal tubule diuretic and osmotic action leading to a reduction in glucose reabsorption, and mild natriuretic and diuretic effects. Following up on these unique effects, several studies showed that treatment with SGLT2i may not only increase the efficacy of standard antidiabetic therapy, but also reduce CVD and HF mortality [5–8].

Until now, the utilization of SGLT2i in Poland has been relatively limited, which has meant there is a lack of experience in their usage, and underutilization in the treatment of patients. Herein, a study with this novel class of drugs is reported in a cohort of 52 Polish DM2 patients with CVD, including a large proportion of patients with HF, all of whom were prescribed SGLT2i.

A retrospective analysis was performed that included 52 diabetic out- or inpatients, who agreed to treatment with SGLT2i between 2017 and 2019. At baseline, all patients underwent a detailed diagnostic work-up: clinical evaluation, blood tests (including NT-proBNP, fasting glucose, HbA1c, cholesterol LDL and creatinine levels), electrocardiogram and echocardiography. Telephone contact or outpatient visits were carried out in December 2019 and January 2020. The investigation conforms to the principles outlined in the Declaration of Helsinki.

All parameters are presented as means ± standard deviation or counts (percentages) when appropriate. All variables were tested for normal distribution of data with the Shapiro-Wilk test. Comparisons of continuous parameters between patients with and without HF were conducted with t-tests when normality was confirmed, or otherwise, with the Mann-Whitney test; the χ^2 test was performed for the comparison of qualitative parameters. All results were considered statistically significant when their p-value was < 0.05. The Statistica package, version 13.0 (StatSoft, TIBCO Software Inc.), was used for the statistical analysis.

Out of 52 patients 50 (96%) received empagliflozin and 2 (4%) dapagliflozin. Most patients (40; 77%) were also treated with metformin, 15 (29%) received insulin and 10 (19%) sulphonylurea. Patients were stratified into those with HF (36.7%) and those without HF (16.3%) (Table 1). Both groups were burdened with a high number

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Table 1. Detailed characteristics of the study population.

Parameter	Patients with HF (n = 36)	Patients without HF (n = 16)	P
Age [years]	64.6 ± 9.0	60.4 ± 13.5	0.47
Male	29 (81%)	10 (63%)	0.32
Heart rate [bpm]	76.3 ± 11.0	73.2 ± 9.9	0.51
Atrial hypertension	31 (86%)	14 (88%)	0.89
Coronary artery disease	27 (75%)	10 (91%)	0.53
Atrial fibrillation	8 (22%)	6 (38%)	0.15
Dyslipidemia	31 (86%)	16 (100%)	0.006
Obesity	18 (58%)	9 (56%)	0.52
Ejection fraction [%]	38 ± 16	57 ± 8	< 0.001
LVEDD [mm]	57 ± 10	51 ± 5	0.03
Fasted glucose [mg/dL]	10.6 ± 4.5	6.7 ± 1.7	< 0.001
HbA1c [%]	8.8 ± 3.1	6.9 ± 1.6	0.48
Creatinine [mg/dL]	110 ± 71	83 ± 11	0.03
LDL cholesterol [mmol/L]	2.8 ± 1.1	2.7 ± 1.4	0.64
Metformin	27 (75%)	13 (81%)	0.86
Insulin	12 (33%)	3 (19%)	0.46
Sulphonylurea	8 (22%)	2 (12.5%)	0.06

All data are presented as means ± standard deviation or counts (percentages). HF — heart failure; LDL — low density lipoprotein; LV — left ventricular end-diastolic diameter

of CVD and CVD risk factors. Fasting glucose was significantly higher in the HF group; however, HbA1c was similar. Understandably, HF patients had larger left ventricles with much worse systolic function. Following SGLT2i initiation, tolerance was very good and there were no complaints of any immediate side effects.

After a follow-up of 16.3 ± 23.6 months, 47 (90%) patients were continuing treatment with SGLT2i. The main reason for SGLT2i discontinuation was the price of the medication (no subsidy in the form of a reimbursement was available). Three (5.8%) patients reported benign urinary tract infection (uncomplicated cystitis or urethritis) during the course of treatment, which resolved itself without major incident (no prolonged antibiotic therapy or hospitalization were required). As for the HF group, their New York Heart Association (NYHA) class improved (baseline: 2.3 ± 0.65 vs. follow-up: 2.0 ± 0.67; p = 0.04), patients reported sustained weight-loss of 4.5 ± 5.6 kg, and required lower daily furosemide dosage (baseline: 56.7 ± ± 20.7 vs. follow-up: 46.7 ± 53.6 mg/day; p = 0.03).

Type 2 diabetes mellitus and CVD, especially CAD and HF, independently contribute to cardiovascular morbidity [2, 3, 9]. They frequently coexist — DM2 is present in up to 45% of HF patients — and HF death is one of the most common causes of death among patients with both CVD and DM2 [3, 10]. Numerous studies published in the last decade have reported on negligible improvement in terms of mortality rates in patients with DM2 and coexisting CVDs. It is only recently that large outcome trials have demonstrated the unprecedented efficacy of SGLT2i in the reduction of major cardiovascular events [5, 6]. Furthermore, it seems that we are on the verge of a paradigm shift in the management of DM2 (with and without CVDs). Therefore, the SGLT2i are a class I recommendation for DM2 patients with high CVD risk in the latest guidelines from the European Society of Cardiology 2019, especially with poor DM2 control [3].

Presented herein, are the first Polish results of treatment with SGLT2i. Overall, there was a very good uptake of this new therapy; in the present study, the SGLT2i was mostly introduced in high-risk patients with CVD which had already been established, of whom a large proportion consisted of HF patients. As for side effects, a very small number of urinary tract infections (an anticipated and previously reported problem due to glucosuria) occurred during the course of treatment (a treatment lasting for more than 2 years for some patients). However, it was slightly more prevalent than in other studies presented (1.5% in

dapagliflozin and 1.7% in empagliflozin analysis) [5, 6]. Moreover, in contrast to those studies there were no genital infections observed in the current population. Reassuringly, substantial improvements were observed in HF patients in terms of symptoms and physical performance (lower NYHA class), sustainable weight reduction, along with a simultaneous reduction in furosemide daily dosage.

Initial experience with a new class of antidiabetic drugs — SGLT2i is very positive and shows results similar to those reported in major trials and registries. The sustainable benefit in the HF subgroup is of particular importance as these patients are particularly prone to complications. As it has recently been announced that the cost of SGLT2i can be reimbursed in Poland (with the application of strict criteria for eligibility), there now seems to be a ray of hope on the horizon for patients with DM2 and CVDs.

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COVID-19-related fatal myocarditis in a 42-year-old female patient

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A 42-year-old female patient was admitted for shortness of breath during the COVID-19 pandemic. She had been tested positive for SARS-CoV-2 5 days before hospital admission. Medical history included bariatric surgery for morbid obesity 6 years prior and elevated blood pressure at occasional measurements. Admission heart rate was 75 bpm and blood pressure was 109/62 mmHg. Body mass index was 42 kg/m^2. C-reactive protein was 54.3 mg/L (0–5 mg/L), high-sensitivity cardiac troponin I level was 12.3 ng/L (< 16 ng/L), lactate dehydrogenase was 464 U/L (120–240 U/L), and N-terminal-pro-B-type natriuretic peptide was 150 pg/mL (< 125 pg/mL). Peripheral oxygen saturation was 82% and increased to 89% with oxygen supply (4 L/min by nasal cannula). Transthoracic echocardiography showed normal systolic left ventricular function. Chest radiography showed bilateral pulmonary infiltrates (Fig. 1A). Electrocardiography revealed T-wave inversion in leads III and aVF and repolarization irregularities in left precordial leads (Fig. 1B). The patient required mechanical ventilation for progressive respiratory failure 6 hours after admission. High-sensitivity troponin I and N-terminal-pro-B-type natriuretic peptide increased to a peak of 28.1 ng/L (< 16 ng/L) and 636.8 pg/mL (< 125 pg/mL), respectively. On day 9 after admission, sudden onset ventricular fibrillation occured (Fig. 1C) and resuscitation was unsucessful. Autopsy revealed lymphocytic infiltates of the myocardium (Fig. 1D) and positive staining with anti-CD3 antibody characterizing T cells (Fig. 1E, F).

Conflict of interest: None declared

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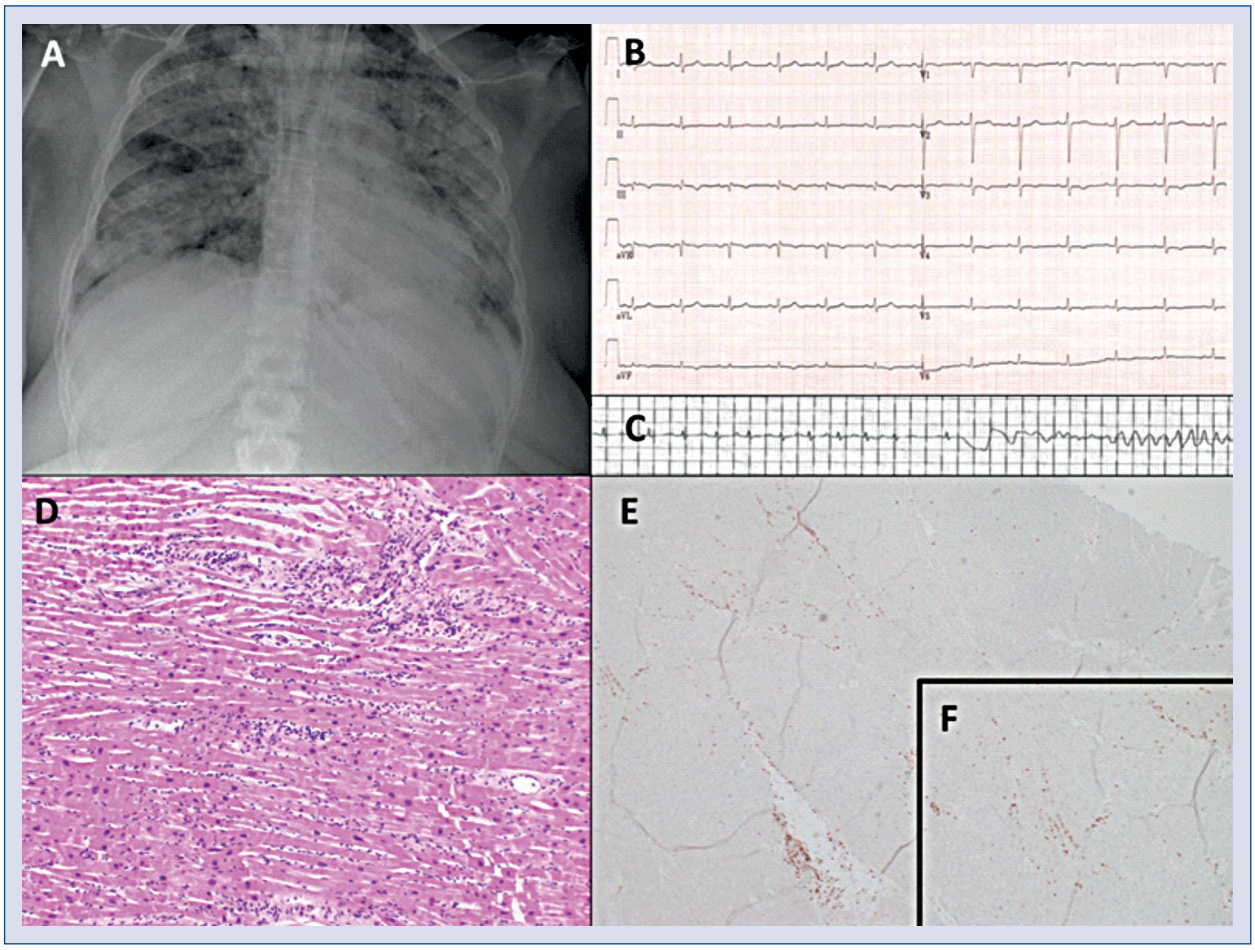

Figure 1. Chest radiography with bilateral pulmonary infiltrates (**A**). Electrocardiography reveals T-wave inversion in leads III and aVF and repolarization irregularities in left precordial leads (**B**). Monitor electrocardiogram with sudden onset ventricular fibrillation (**C**). Hematoxylin-eosin staining of myocardium reveals lmphocytic infiltates (**D**) with positive staining with anti-CD3 antibody characterizing T cells (**E, F**).

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Three coronary arteries arising from one coronary cusp

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A 53-year-old man with a history of hypertension and hyperlipidemia presented to the emergency department with central chest pain. An electrocardiogram showed ST-segment elevations in the inferior leads and ST-segment depressions in leads V1–V3 consistent with an infero-posterior ST-segment elevation myocardial infarction. Emergency coronary angiography was performed. There was difficulty cannulating the left main artery in the left aortic sinus with JL4 and JL3.5 catheters. The right coronary ostium was engaged with a JR4 catheter. This demonstrated a superdominant right coronary artery (RCA, ®) with a thrombotic occlusion in the mid-vessel and both the left anterior descending (LAD, @) and left circumflex (LCx, ©) arteries arising from the right coronary ostium (Fig. 1A, **Suppl. Video 1**, right anterior oblique projection). Primary percutaneous coronary intervention to the mid-RCA was performed with excellent results (Fig. 1B). The LAD and LCx arteries had minor irregularities. A computed tomographic coronary angiogram subsequently demonstrated RCA, LAD and LCx originating from the right coronary cusp with side-by-side origins. The RCA was the first branch from the right lateral aspect, followed by the LAD and the LCx left laterally (Fig. 1C1, C2 and C3; three-dimensional reconstruction, white arrow indicates stented segment; Fig. 1D; multiplanar reformation). The patient's medical therapy was optimized and he was discharged uneventfully. Anomalous coronary artery from the opposite sinus is a rare finding, especially when relating to left coronary arteries. It has been associated with early atherosclerosis, myocardial ischemia and sudden cardiac death.

Conflict of interest: None declared

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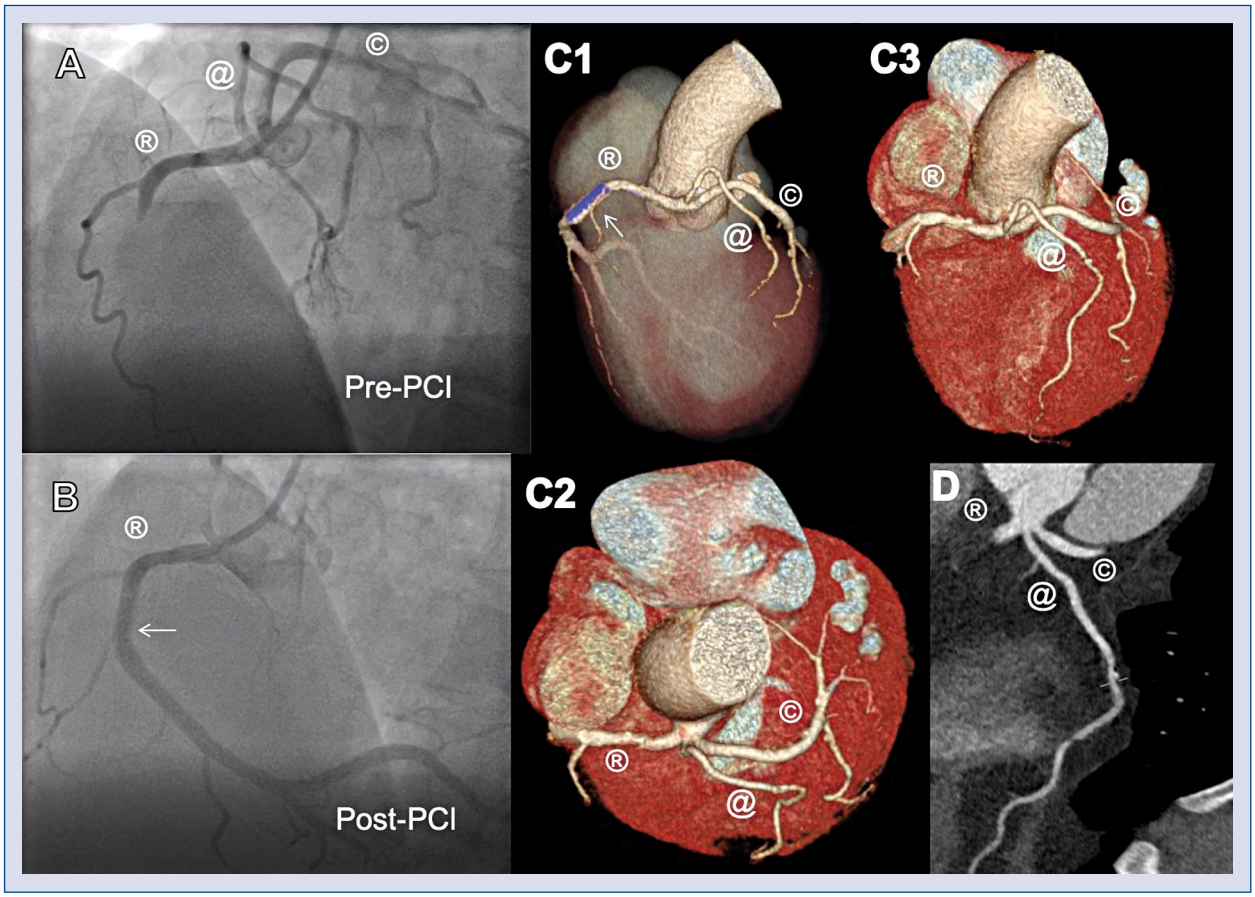

Figure 1. Coronary angiography pre-percutaneous coronary intervention (**A**) and post-percutaneous coronary intervention (**B**). Computed tomography coronary angiography showing right coronary artery, left anterior descending artery and left circumflex artery arising from the right coronary cusp on three-dimensional reconstruction (**C1**, **C2**, **C3**; white arrow indicates stented segment) and multiplanar reformation (**D**).

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Percutaneous retrieval of patient-cut-of central venous catheter: Fishing with a pigtail and a goose-neck

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A 57-year-old patient was admitted for percutaneous retrieval of a fragment of a central venous catheter. The patient was originally treated in an intensive care unit for acute alcoholic pancreatitis with septic shock and had a central venous line placed into the right subclavian vein. In the course of delirium tremens, the patient cut off a piece of a catheter, while the remaining part migrated into the vascular system.

A chest X-ray and echocardiography revealed the presence of a foreign body within the right ventricle and inferior vena cava (IVC) (Fig. 1B). Computed tomography confirmed the location of the catheter (Fig. 1A). The distal fragment was wedged within the right ventricular trabeculation, while the proximal — in the bifurcation of IVC and hepatic vein.

Through the right femoral vein, Flexor Ansel Guiding Sheath 12 F was inserted up to IVC. After several attempts of repositioning the foreign body with a guidewire (Fig. 1C) and a snare (no free end to catch with a loop), it was relocated with a pigtail, looped and was pulled it back into IVC (Fig. 1D). Holding the catheter with the pigtail, a free end of the catheter was caught with an Amplaz GooseNeck Snare. The pigtail was then removed, the catheter trapped by a loop-snare was pulled into the sheath and entire system was removed.

Although percutaneous foreign body retrieval may have complications (perforation, tamponade) a loop-snare technique should be an approach of choice. Using large, long sheaths allows delivering the tools precisely to the site and ensures safe and easy withdrawal of a foreign body.

Conflict of interest: None declared

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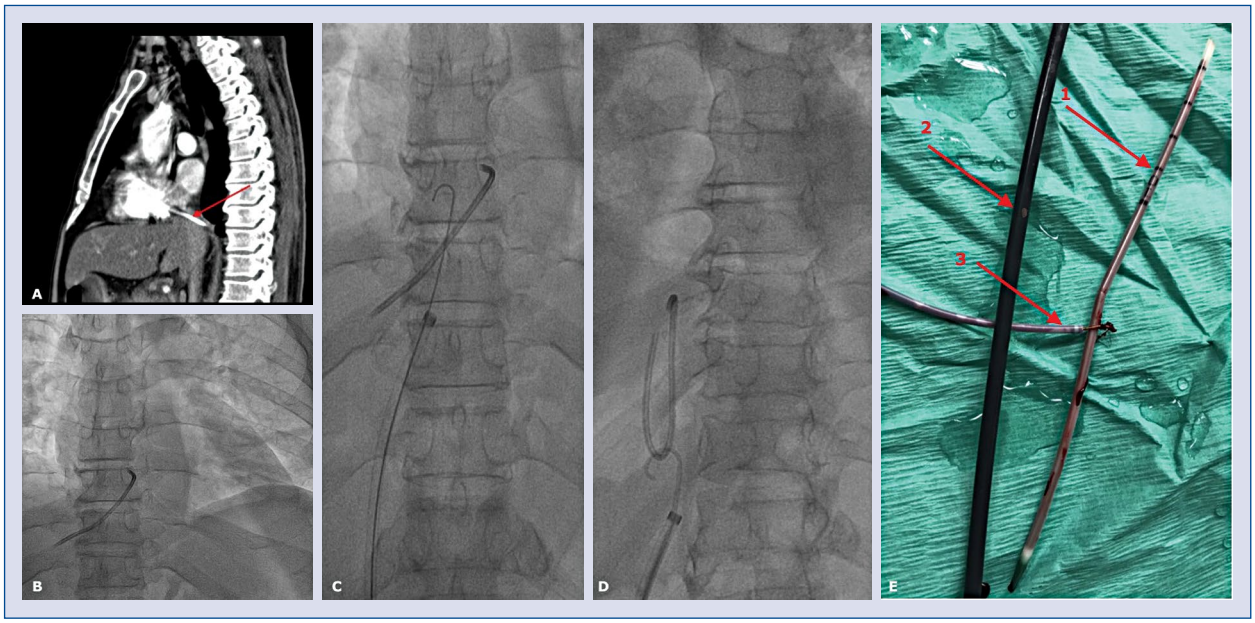

Figure 1. A. Computed tomography (sagittal plane) — red arrow pointing catheter in inferior vena cava (IVC); **B.** Chest X-ray (AP, section); a long radiopaque fragment of catheter from right heart to IVC; **C.** 12 F sheath inserted from femoral vein up to IVC; **D.** Catether grasped by a pigtail catether, folded and pulled into IVC; distal end inleashed; **E.** After procedure: removed 13 cm catether fragment (1), trapped by Amplatz snare (3) next to 12 F sheath (2).

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Cutting and partially retrieving an entrapped guidewire using a novel retrograde rotablation technique

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A 52-year-old man was referred to the documented hospital because a SION guidewire was entrapped during percutaneous coronary intervention of the right coronary artery chronic total occlusion in a local hospital. The initial attempt was to retrieve the guidewire with the support of microcatheter and balloon, but this ended in failure. The patient refused emergent open surgery. It had been over 6 hours since the right coronary artery percutaneous coronary intervention attempt and the patient became uncooperative. Thus, the plan was to cut and partially retrieve the entrapped guidewire using a novel retrograde rotablation technique. The procedure was as follows: 1. Disengaged the initial guiding catheter (GC). A second GC was used to approach the initial GC. 2. A workhorse guidewire was retrogradely advanced into the initial GC. Trapped the retrograde guidewire using a semi-compliant balloon and tried to bring the two GC as close as possible. 3. Advanced a floppy rotawire from the second GC into the initial GC. Then initiated rotablation at the tip of the initial GC. After the retrograde rotablation procedure, the entrapped guidewire was fractured and then partially retrieved (Fig. 1). Entrapment of guidewire is a rare complication of percutaneous coronary interventions. Dr. Jae Young Cho and Soon Jun Hong reported the first case of cutting the entrapped guidewire using rotational atherectomy device in 2017. The present case highlights a novel method for cutting and retrieving entrapped guidewires using a retrograde rotablation technique. In the application of this technique, the rotablation is performed in GC rather than the coronary artery, thus being safer and more efficient.

Conflict of interest: None declared

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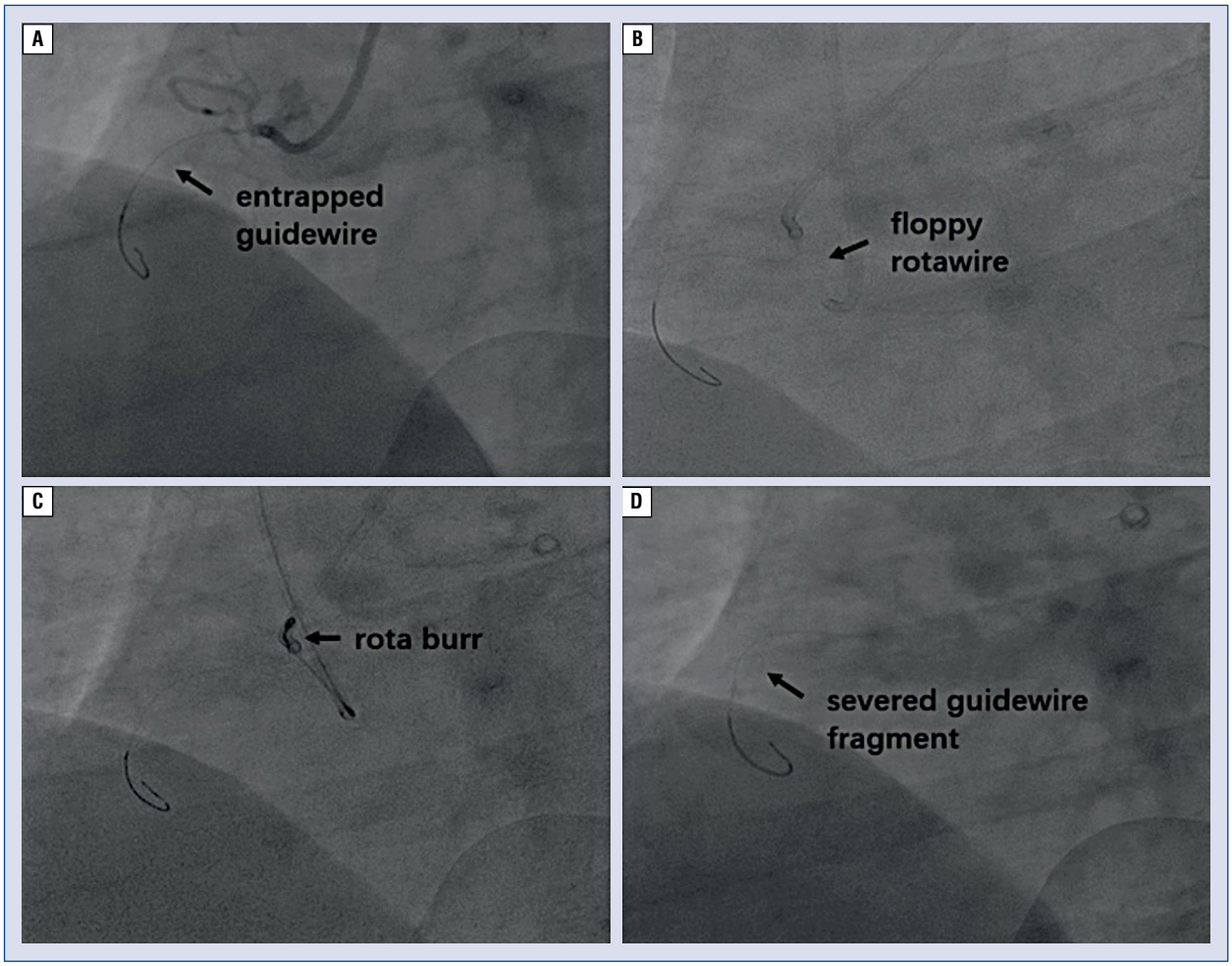

Figure 1. The procedure of cutting and retrieving an entrapped guidewire using a novel retrograde rotablation technique. **A.** A SION guidewire was entrapped during percutaneous coronary interventions of right coronary artery chronic total occlusion (CTO); **B.** Advanced a floppy rotawire from the second guiding catheter (GC) into the initial GC; **C.** Then initiated rotablation at the tip of the initial GC; **D.** After the retrograde rotablation procedure, the entrapped guidewire was fractured and retrieved, while the severed guidewire fragment was retained within the CTO lesion.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

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A thrombus migrating from the left femoral--popliteal deep vein through the right atrium leading to a massive pulmonary embolism

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A 99-year-old male, without relevant past medical history presented to the emergency department for syncope. On arrival he was in shock with hypotension, tachycardia and cold extremities. 36% FIO2 were necessary to reach normal oxygen saturation. Arterial blood gas revealed a lactic acidosis with pH 7.1. Electrocardiogram showed sinus tachycardia and right bundle branch block. A focused cardiac ultrasound was performed revealing a voluminous and highly mobile thrombus in the right atrium moving through the tricuspid valve during diastole (Fig. 1, **Suppl. Video 1**). The right ventricle was dilated and presented systolic dysfunction with free wall hypokinesia. Anticoagulation by bolus of intravenous heparine and intravascular volume were administered immediately. Focused cardiac ultrasound was repeated a few minutes later due to clinical worsening. The thrombus was absent and the exam highlighted a more severely dilated and dysfunctional right ventricle with a systolodiastolic flattening of the interventricular septum, suggesting a massive pulmonary embolism due to thrombus migration. Intravenous thrombolysis with a half dose alteplase due to his advanced age was performed.

The patient was admitted to intermediate care with a rapid resolution of shock and improvement of hypoxemia. An echo-Doppler of inferior limbs showed a left femoral-popliteal deep venous thrombosis, revealing the most likely origin of the thrombus. Pulmonary embolism was confirmed by computed tomography angiography, performed due to a worsening thoracic pain.

The patient celebrated his 100th birthday in hospital and was transferred a few days later to a clinic for convalescence.

This case highlights the value of focused cardiac ultrasound for clinical decision making in hemodynamic unstable patients.

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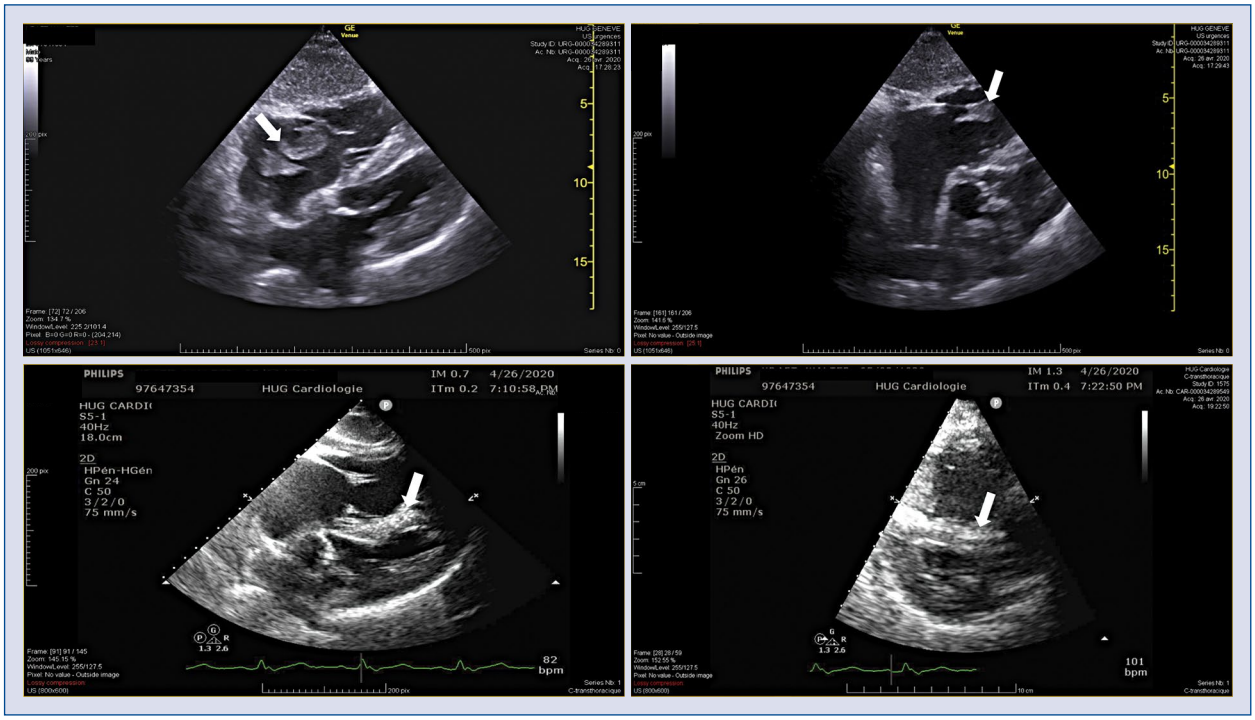

Figure 1. First (**upper panels**) and second (**lower panels**) focused cardiac ultrasound. **Upper panels:** First focused cardiac ultrasound revealing the thrombus in the right atrium (white arrow) moving in the right ventricle through the tricuspid valve (right upper panel). **Lower panels:** Second focused cardiac ultrasound showing the absence of the thrombus with a clear systolodiastolic flattening of the interventricular septum (white arrow) in subcostal four-chamber view (left lower panel) and parasternal short-axis view (right lower panel).

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

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Implantation of a leadless pacemaker in a young adult patient with repaired tetralogy of Fallot

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Reported herein, is the case of 21-year-old patient with repaired tetralogy of Fallot within her first year of life. Due to sick sinus syndrome and II grade atrioventricular block endocardial single-chamber permanent pacemaker was inserted transvenously during her third year of life.

The patient was admitted in generally good condition aiming at pacemaker replacement. Right ventricle lead dysfunction was observed and thus, percutaneously removing and implantation of a new electrode was planned. Angio-computed tomography showed an obstruction of the superior vena cava. Pacemaker generator and lead were removed percutaneously but it was not possible to implant a new lead. The patient was managed with temporary transvenous pacing. The Heart Team qualified the patient for implantation of a leadless pacemaker (the Micra™ Transcatheter Pacing System, Medtronic, Minneapolis, MN, USA).

Implantation of the Micra™ was performed under general anesthesia. Access via the right femoral vein was obtained with 23 Fr sheaths. Micra™ was fixed into upper part of the interventricular septum (Fig. 1). Implant parameters were optimal with 8.2 mV sensing, 650 Ohm electrode impedance and pacing threshold 0.5 V/0.24 ms. There were no complications. The time of fluoroscopy was 13 min, and exposition dose was 864 mGy.

The patient was discharged receiving beta-blocker. The pacing threshold increased, reaching a maximum of 3.5 V at 0.24 ms during the first, and second month post-implantation. At 3-month follow-up pacing threshold decreased below 3.0 V/0.24 ms and was stabile until the 21-month follow-up. Other parameters were stable during follow-up. The stimulation percentage ranged from 1% to 12.8%.

Conflict of interest: Beata Średniawa — consultant: Medtronic, Zoll, Bayer, lectures fee for: Boehringer-Ingelheim, Bayer, Pfizer; Ewa Jędrzejczyk-Patej — consultant fees from Medtronic, Biotronik, Abbott, Boston Scientific; Zbigniew Kalarus — company sponsored speaker's bureau from Pfizer, Eli Lilly, Boehringer-Ingelheim, Abbott, Bayer; travel expenses to cardiology congresses from St. Jude Medical and Adamed; advisory committee: Boehringer-Ingelheim, Amgen, AstraZeneca.

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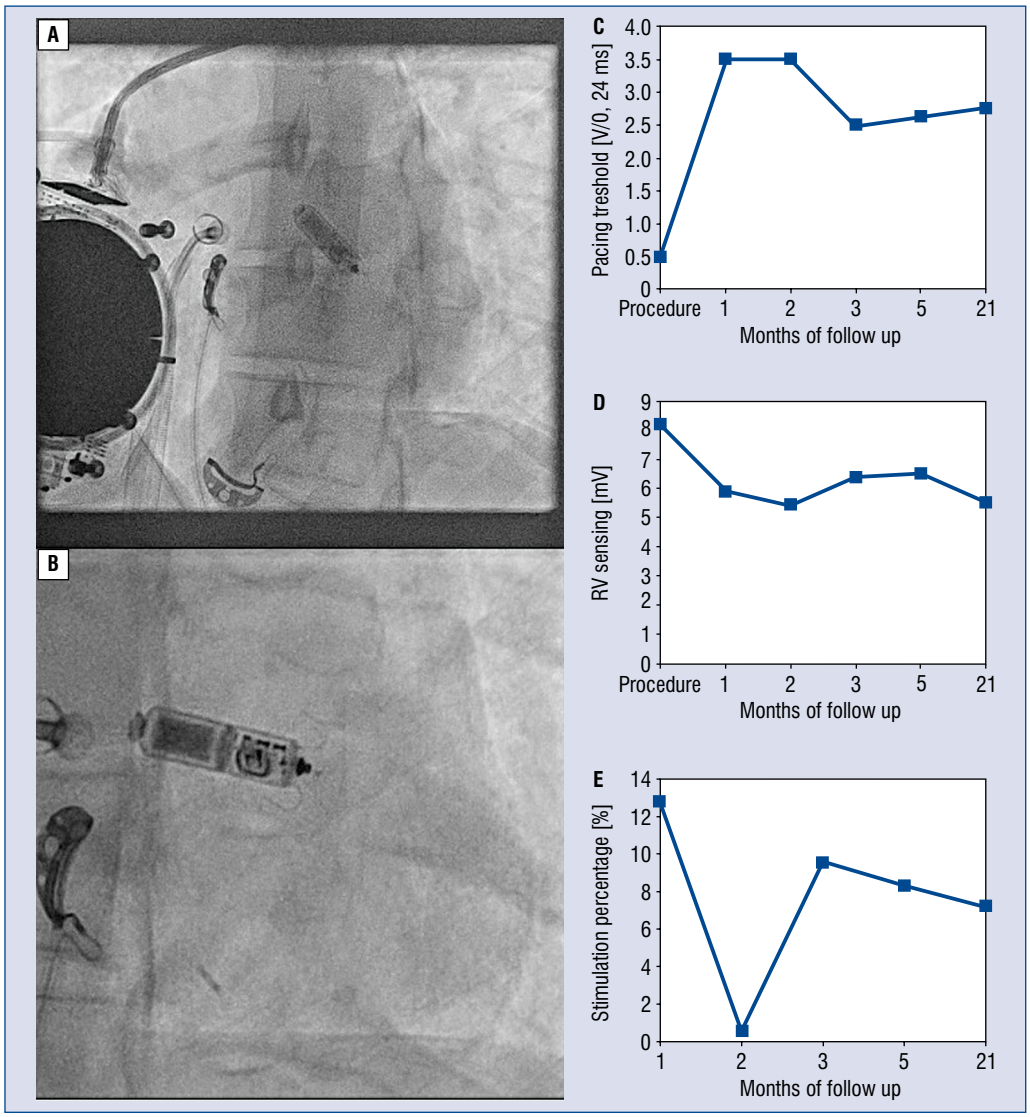

Figure 1. Location of the Micra™ device in fluoroscopy during the implantation procedure (**A**, **B**). Electrical parameters of the device: right ventricle (RV) pacing threshold (**C**), RV sensing (**D**), stimulation percentage (**E**).

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Multimodality imaging of a congenital left ventricular diverticulum

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A 58-year-old woman presented to her primary care physician with acute-onset diffuse abdominal pain. A computed tomography scan of the abdomen did not reveal any abdominal abnormalities. It incidentally showed an outpouching in the inferolateral wall of the left cardiac ventricle toward the base (Fig. 1A). Transthoracic echocardiography revealed an inferolateral basal left ventricular outpouching with calcified rims (Fig. 1B, C). No ischemic workup was pursued given that the patient was asymptomatic. A contrast-enhanced cardiac magnetic resonance imaging was obtained for structural and functional assessment of the outpouching. It showed a broad-based outpouching with dyskinesia involving the basal inferolateral wall without associated filling defects or delayed enhancement (Fig. 1D). The appearance of the imaging was typical of a congenital diverticulum. The patient was then reassured and managed conservatively.

Congenital ventricular diverticula are rare cardiac malformations and their diagnosis usually requires a multimodality approach. A typical congenital diverticulum contains all layers of the ventricular wall (endocardium, myocardium, and pericardium) and contracts in synchrony with the surrounding myocardium whereas a left ventricular aneurysm does not contract. The present case underlines the importance of multimodality imaging in narrowing down the differential diagnosis of cardiac outpouchings and diagnosing congenital cardiac diverticula.

Conflict of interest: None declared

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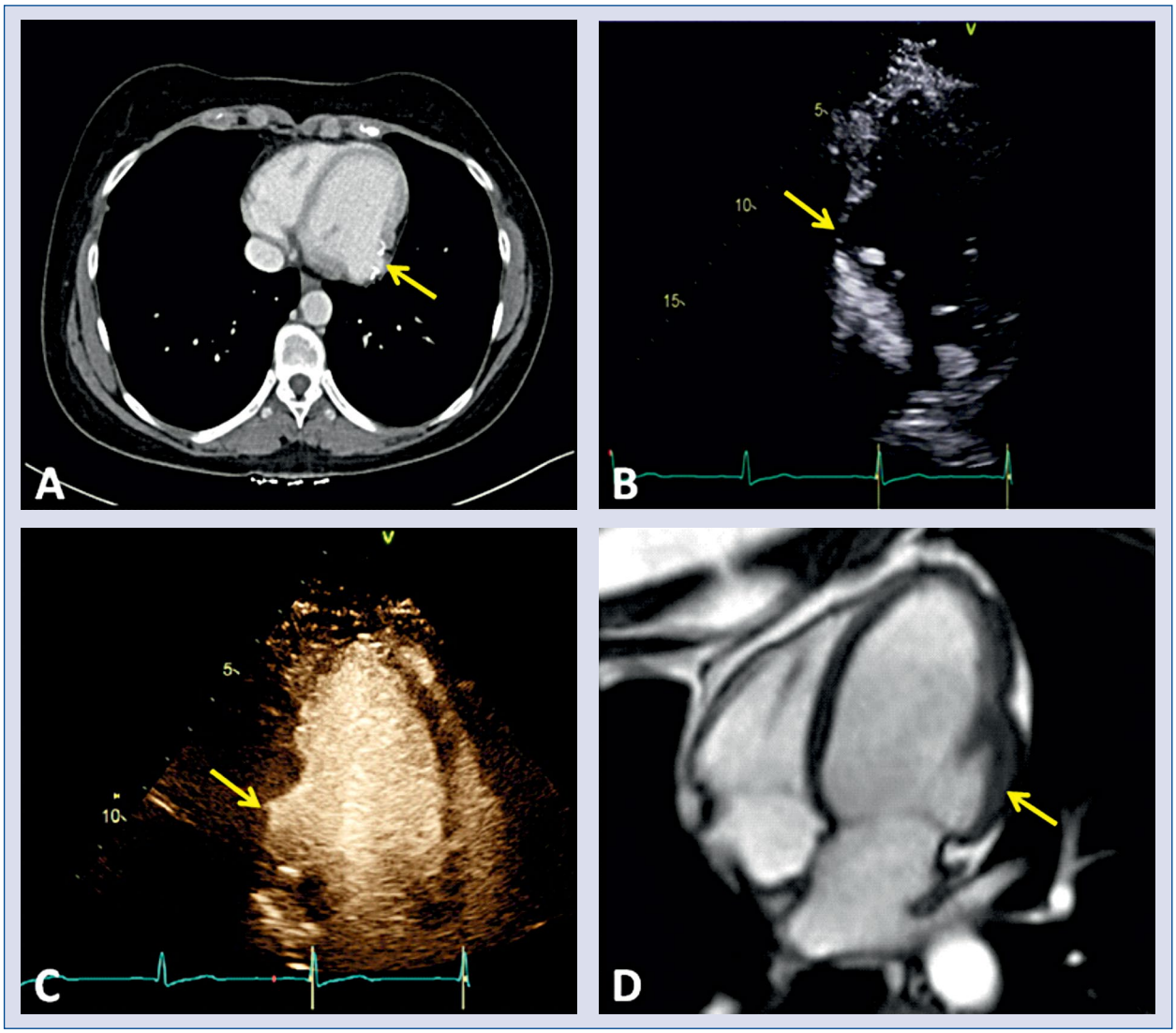

Figure 1. An abdominal computed tomography scan (**A**), transthoracic echocardiography (**B**, **C**), and cardiac magnetic resonance imaging (**D**) showing a left ventricular outpouching typical of a congenital diverticulum.

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LETTER TO THE EDITOR

Resuscitation in COVID-19 patients: What do we know and what should we do?

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Recent articles on cardiopulmonary resuscitation (CPR) in coronavirus disease 2019 (COVID-19) patients [1, 2] were read with great interest.

It was concurred herein, that automated chest compression devices (ACCD) should be added to cardiopulmonary resuscitation (CPR) protocols in pandemic and these data are welcomed [1]. However, presently it was not considered right to leave the decision of CPR for the elderly with initial non-shockable rhythms to individual therapeutic teams [2]. In addition to a self-fulfilling prophecy risk, the effect of self-protection behavior of decision makers on the decision-making process may create less aggressive medical management risk than it should be. The present article discusses both strategies proposed for the CPR decision and management after the return of spontaneous circulation.

Resistant hypoxemia secondary to viral pneumonia associated acute respiratory distress syndrome, primary viral or secondary myocardial injury, serious ventricular arrhythmias, and shock are considered among the leading reasons of in-hospital cardiac arrest and the resulting mortality [3]. In patients diagnosed with or suspected to have COVID-19, CPR poses a certain risk to healthcare professionals due to excessive air droplet scattering (aerosolization) during the procedure.

Reports during the pandemic period have indicated that the survival rate after CPR is lower and the neurological prognosis is worse in COVID-19 cases, in comparison to a non-pandemic era [4]. Reasons may include admission of patients with severe COVID-19 to regular floor beds due to the scarcity of intensive care beds and high ventilator occupancy, a delay in initiation of resuscitation due to time lost while wearing personal protective equipment, suboptimal quality of resuscitation, and a more predominant role of respiratory failure as the cause of arrest. Moreover, the prevalence of out-of-hospital cardiac arrest (OHCA) has also increased during the pandemic [5]. Rates of not only survival but also favorable prognosis have deteriorated in OHCA compared to the previous data, probably due to prolonged transport time of patients to hospitals and lower rate of resuscitation by lay persons at the scene.

The general principles of the recent resuscitation guidelines in pandemic, which highlight certain algorithmic adaptations to enhance the protection of the resuscitator during basic/advanced cardiovascular life support, are noteworthy. However, it is not known whether these adaptations would positively or negatively affect the survival rates observed after CPR in this era. In addition, there are insufficient data to support the use of extracorporeal CPR and targeted temperature management in COVID-19 patients. It is also known that induced hypothermia in severe sepsis is potentially harmful [6], and considering that these invasive methods are not widely applicable, it can be predicted that COVID-19 CPR survivors will not be amenable for these therapies in the current global resource-limiting setting.

As for all post-CPR patients, in comatose COVID-19 survivors, one of the main critical issues is the determination of neurological prognosis after the return of spontaneous circulation. However, recent interim guidelines do not address this issue. The present article shares opinions and concerns on neuroprognostication of patients who survived in a comatose state after CPR, also called as post-resuscitation encephalopathy (PRE).

First of all, "neurological examination" is crucial in establishing neuroprognostication in COVID-19 patients with PRE [7]. In theory, a bed-side neurological examination will assess the extent of the neuro-anatomical injury to some degree, especially if performed by an experienced neurointensivist. In the examination performed

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72 h after return of spontaneous circulation, the absence of pupillary reactions and no better than decerebrating motor response to painful stimuli are highly reliable prognostic markers of poor prognosis [8]. During this period, an absence of the corneal reflex, presence of up-ward eye deviation and myoclonic jerks are also helpful in prognostification. However, in the last decade, problems related to performing prognostification with "only" neurological examination have repeatedly been emphasized. It is underlined that the examination may not be objective under confounding factors like hypothermia, sedation, muscle relaxants and hemodynamic instability, and estimations suggestive of poor outcomes could inadvertently lead to a self-fulfilling prophecy when making individual decisions for the patient. The lack of blinding in most of the studies focusing on prognosis, very low sensitivity of neurologic examination findings, and probably the not so high specificity of these measures in a real-life setting, probably underlie the cautious statements in this regard [7].

At this point, it should be noted that the majority of post-arrest deaths is due to the cessation or withdrawal of "active" of life-sustaining treatments, which is primarily driven by the decision of poor prognosis based on examination [7]. A chaotic setting like the current pandemic, might put more pressure on doctors experiencing difficulties for booking an intensive care unit bed, and might force them to stop life-sustaining treatments earlier. However, even leaving aside the discussions in the general population, it should not be forgotten that the accuracy of these prognostic models, and thereby the decisions for continuation or withdrawal of care, have not been investigated properly in COVID-19 patients. In addition, it is also not known how these patients would recover in the long run after appropriate care.

A multitude of questions are still unanswered regarding the prognostic models for COVID-19 patients. Could it be useful to incorporate biomarkers such as neuron-specific enolase, electrophysiology such as electroencephalographic reactivity, or imaging tools such as diffusion-weighted magnetic resonance imaging (DWI) to algorithms to increase the accuracy of decisions in COVID-19 patients with PRE? Can the presence of widespread ischemic damage detected in DWI be performed between the second and fifth days after successful CPR guide the prognosis [9]? Pure hypoxemia and global cerebral ischemia are also said to show different patterns in DWI, would it be helpful [10]? And the list goes on.

It should not be forgotten that albeit COVID-19 might follow a serious course, it is not a terminal disease, most patients can be saved with good critical care support, and these patients deserve the standard of care during and after cardiac arrest. It is without doubt that we need to study neuroprognostification in COVID-19 patients with PRE, within a short time and without further delay. Until this is achieved, physicians in the front-line, need precise expert opinions and guidelines, as they continue to employ prudent decisions without swerving from scientific principles, as always.

Conflict of interest: None declared

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VIA MEDICA

LETTER TO THE EDITOR

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Resuscitation in COVID-19 pandemic. Authors' replay

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In response to the letter to the editor [1] referring to two of our articles [2, 3], we would like to present our perspective. First of all, we believe that every patient has the right to the best medical care according to the highest standards. Decisions on whether or not to undertake resuscitation procedures are always difficult and require critical clinical experience. During the time of the COIVD-19 threat, especially in the early stages of the pandemic, where the course of the elderly was particularly severe and often fatal, forced us to assess the risk of an action for medical personnel.

Correct, good quality chest compression during cardiopulmonary resuscitation (CPR) operations in adults is extremely demanding in terms of workload and physical effort of the rescuer. The use of personal protective equipment according to many sources and our own professional experience will limit the possibility of performing high-quality CPR activities.

While thanking you for your comments, we also believe that the use of mechanical chest compression is important and may affect the survival of patients, especially in the case of long-term resuscitation. In a pandemic situation, it can be a particular convenience when conducting resuscitation activities.

With regard to remarks concerning the undertaking of long-term resuscitation activities in elderly people with non-shockable rhythms, we present the following remarks. The decision on resuscitation of elderly patients with initial non-shockable rhythms should, in our opinion, be left to the CPR team. Considering the extremely low effectiveness of COVID-19 patients' resuscitation activities in the case of non-shockable rhythms in COVID-19 and confronting it with the scope and duration of the activities as well as the involvement of the medical personnel, such a decision should be made individually in each case. In our articles, we have shown the results of the treatment of patients with sudden cardiac arrest in COVID-19. The extremely low effectiveness of resuscitation in patients with non-shockable rhythms is remarkable. One of the basic tasks in both basic and advanced resuscitation activities is to provide safety for the rescuers — medical personnel according to European Resuscitation Council (ERC) and American Heart Association (AHA) guidelines. In the case of a pandemic, and especially in the case of an extremely high demand for rescue and intensive care activities with a huge shortage of qualified medical personnel, the decision on resuscitation should be left to individual therapeutic teams. When analyzing the risk for medical personnel, it is necessary to take into account the need to perform activities using full protection — personal protective equipment. Carrying out such intensive medical activities, including chest compressions for a period of several dozen minutes even when changing rescuers is extremely demanding [4]. It is also important to remember about the oxygen demand in rescuers during such extremely physically demanding operations. Carrying out such a long resuscitation in protective equipment, due to problems with a rescuer's ventilation, body tem-

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perature and other factors influencing his physical performance should be taken into account.

Our aim was not to question, in the slightest the patient's right to the best medical care according to standards. However, in a situation of a serious epidemiological threat, during dramatic emergency department operations, even in the case of more than 1 patient at the same time with extreme shortages of medical personnel, it makes us think about the advisability of some actions concerning the expected benefits.

Conflict of interest: None declared

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