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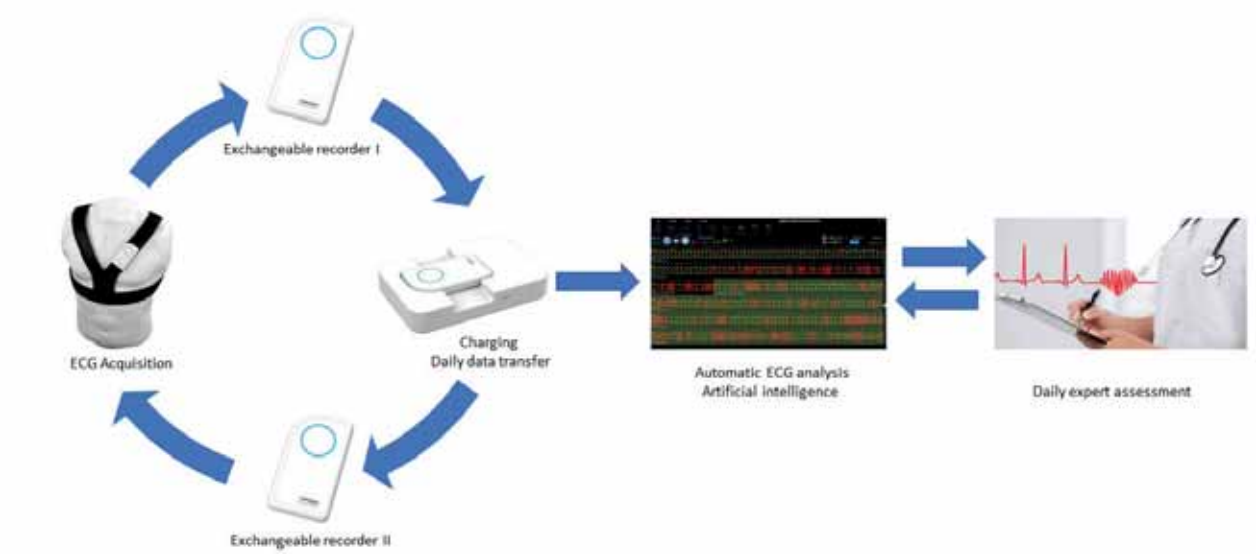

The scheme of the atrial fibrillation monitoring system used in the cross-sectional NOMED-AF study, see p. 16

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CLINICAL VIGNETTE

EXPERT OPINION

Screening for atrial fibrillation: Different approaches targeted to reduce ischemic stroke

Giuseppe Boriani[1], Jacopo F Imberti[1, 2], Marco Vitolo[1, 2]

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Related article
by Kalarus et al.

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In the current issue of *Kardiologia Polska* (*Kardiol Pol*, *Polish Heart Journal*), Kalarus et al. [1] report on the NOMED-AF study that evaluated the prevalence of atrial fibrillation (AF) in a sample of the elderly Polish population. This cross-sectional study was performed between 2017 and 2018 on a random sample of 3014 Polish citizens aged ≥65 years, and enrollment was appropriately planned based on geographical and age strata. This scientific contribution is very interesting since it reports on population screening to detect AF based on prolonged cardiac monitoring using a 30-day Holter, which results in a mean duration of rhythm monitoring of 21.9 days [1]. The study found an overall prevalence of AF, defined as AF lasting >30 seconds, of 19.2%, corresponding either to cases of newly diagnosed AF (4.1% prevalence) or cases of previously diagnosed AF (15.1% prevalence). It is noteworthy that in around 20% of the population, AF was underdiagnosed on the basis of medical history alone. This situation occurred also in patients with prior stroke, a setting where detection of AF is very important in preventing recurrences of cardioembolic stroke, which has serious implications for both patients and healthcare systems [2, 3].

The Holter methods applied in the NOMED-AF study allowed continuous monitoring of the cardiac rhythm for 3–4 weeks, and therefore the possibility to detect AF was greatly enhanced as compared to protocols for AF screening based on single-time point screening with hand-held single lead electrocardiography (ECG) devices [4, 5]. The increased diagnostic capabilities of detection of paroxysmal AF can be easily appreciated by considering that in the NOMED-AF study, only 51% of newly detected cases of paroxysmal AF were diagnosed during the first week of recording, while the others were detected in the following weeks. Furthermore, data analysis highlights that the number of newly diagnosed paroxysmal AF was 7-fold higher thanks to ECG monitoring extended for 4 weeks versus 24 hours [1]. This finding is not surprising since it is linked to the dynamic nature of AF and the variable burden of AF [6] and has obvious implications for the potential diagnostic yield of single time-point ECG recording tools versus tools for more prolonged rhythm monitoring [4].

The authors of the NOMED-AF study have to be congratulated for having planned AF screening based on a very comprehensive approach, including also patients with disabling illnesses or dementia, visited at home, thus overcoming the limitations linked to lack of digital literacy, which the use of wearables and digital tools necessarily implies [7].

Atrial fibrillation screening can be done with different approaches, with systematic screening and opportunistic screening presenting a different impact in terms of organization. Moreover, the potential implementation in daily practice of AF screening, specifically when using digital tools, in both cases entails consideration of a series of issues related to data protection, legal aspects, and reimbursement [4, 8]. NOMED-AF was a large-scale national project performed in Poland on several thousands of patients, and similar initiatives and screening projects, such as

STROKESTOP [9], require important investments in terms of personnel and organized pathways for patient evaluation, which makes it problematic to predict in what specific ways AF screening may become a standard practice and how it can be extensively applied in communities. Whatever the approach to AF screening, it is important to apply a defined clinical pathway for managing patients who have positive tests at AF screening, as shown in Figure 1, including a series of steps based on recommendations by consensus guidelines [2, 3].

As a matter of fact, the planning of AF screening programs implies considering the type of screening (systematic or opportunistic), including the choice of specific technologies and digital devices for checking the cardiac rhythm, taking into account the setting of screening, age of the candidates, associated comorbidities, level of education, cognitive status, and digital literacy [4, 7, 8]. Patient targeting may be important to maximize the chance of detecting AF, which is a difficult balance between the possibility to maximize sensitivity and the problems linked to managing a large number of subjects. A series of criteria for patient targeting can be applied, including age, CHA_2DS_2-VASc, or CHA_2DS_2-VA [5], but also biomarkers such as brain natriuretic peptide (BNP) or N-terminal pro-BNP peptide (NT-proBNP) [4, 10, 11]. We think that the large amount of data collected in NOMED-AF deserves further analysis to assess the potential for specific targeting of candidates to AF screening based on clinical criteria (age, CHA_2DS_2-VASc) or biomarkers (NT-proBNP was measured in the study to assess the possibilities to maximize the feasibility of screening programs in daily practice) [5].

The primary aim of a screening program for AF detection is to identify previously unknown or untreated cases of AF, usually asymptomatic, and to prescribe oral anticoagulants in patients at risk, according to the risk stratification for stroke [2, 3]. This objective is supported by evidence that asymptomatic and symptomatic AF are associated with the same risk of stroke and thromboembolic events [12] and that the risk of stroke associated with single time-point ECG screen-detected AF is high enough to warrant treatment with oral anticoagulants, to effectively reduce the occurrence of stroke and thromboembolic events [13].

The STROKESTOP study was the largest randomized trial evaluating outcome implications of systematic screening of AF and involved almost 30 000 people, aged 75–76 years, who were randomized to receive, or not, an invitation for AF screening, performed using a handheld ECG with recordings twice a day for 14 days [9]. Only around 50% of those invited for screening actually participated, and this influenced the outcomes since the overall results showed a small net benefit on hard outcomes among patients invited to screening compared with the standard of care. Even if the analysis was limited to individuals who actually participated, the program showed a 24% relative risk reduction in ischemic stroke [9].

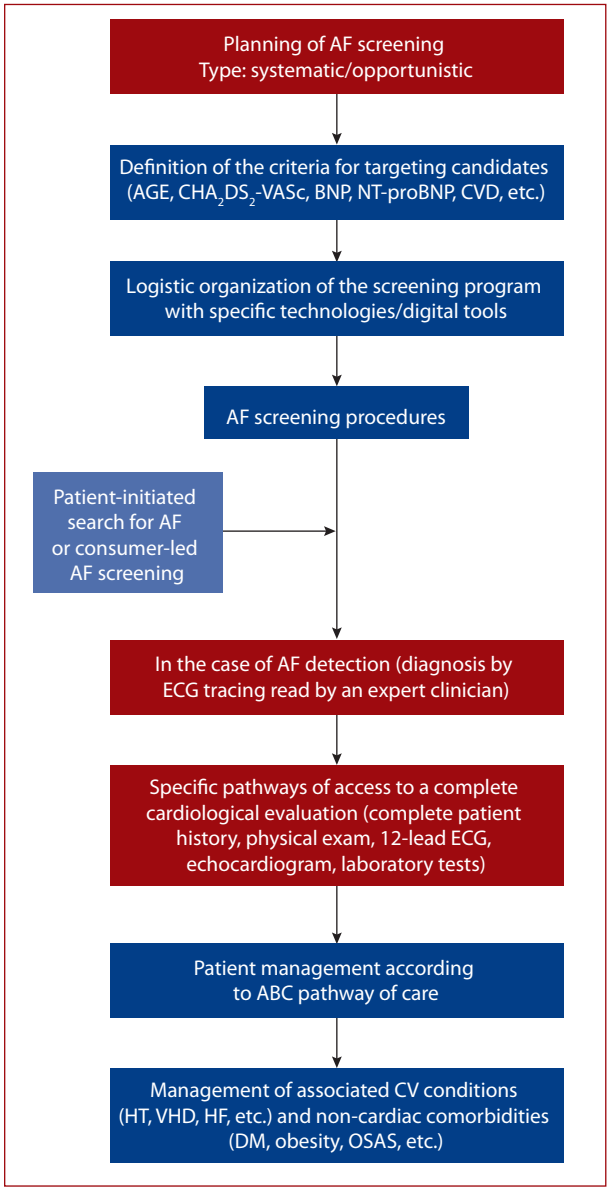

Figure 1. Organization of AF screening, with appropriate clinical pathways for patient evaluation and decision-making

Abbreviations: AF, atrial fibrillation; BNP, brain natriuretic peptide; CV, cardiovascular, CVD, cardiovascular disease; DM, diabetes mellitus; HF, heart failure; HT, hypertension; OSAS, obstructive sleep apnea syndrome; VHD, valvular heart disease

The field of AF screening is still characterized by some controversy on the net benefits associated with treatment with oral anticoagulants in patients at risk of stroke with AF detected during screening. A systematic review by the US Preventive Services Task Force, performed on 26 studies, concluded that the current evidence is insufficient to assess the actual balance of benefits and harms for AF screening [14]. The document delivered by the US Preventive Services Task Force recognized that in patients with screening-detected AF, prescription of anticoagulants was associated with a lower risk of first stroke and mortality, but it also reports that the increased risk of major bleed-

ing requires additional evaluations [14]. Given the current status of knowledge, we personally think, following many guidelines, that AF screening has to be recommended for subjects aged ≥65, but all screening candidates should be adequately informed on the scopes and implications of searching and detecting AF.

The increasing interest in AF screening is well-founded since reducing the burden of AF-associated stroke is a priority for healthcare systems, and the target can be achieved by different methods and approaches. It is crucial to consider appropriate organization, not only for the initial phases of screening but also for the following steps, with specific pathways for the necessary medical evaluation of AF and associated conditions finally leading to prescription of oral anticoagulants when appropriate (Figure 1). In this regard, also the emerging trend towards consumer-led screening, using smartphones or smartwatches [15], should be appropriately managed by clinicians, with the same integrated clinical approach.

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The long wave of COVID-19: Persisting effects on acute coronary syndromes' incidence, management, and outcomes

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Related article
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The COVID-19 pandemic deeply impacted the organization of healthcare systems all over the world. In order to effectively face the pandemic, healthcare systems implemented strategies to optimize diagnostic and treatment pathways, which resulted in a shift of resources towards the management of patients with COVID-19 and penalizing other elective and acute conditions [1]. Among many others, these included invasive cardiology procedures such as diagnostic coronary angiographies and elective percutaneous coronary interventions (PCI) in patients with known or suspected acute or chronic coronary syndromes (ACS). In addition to the predictable reduction of planned procedures, a significant decline in primary PCIs for ACS was reported during the COVID-19 outbreak in Europe, America, and Asia [2–4]. Data from all over the world are consistent and report the hospitalization rate for ACS decreased by up to 50%, with a detrimental impact on survival after ACS [2].

One of the main explanations for this phenomenon is people's fear of contagion, which strongly discouraged attendance at emergency departments (EDs). It is plausible that patients, consciously or unconsciously, underestimated or ignored symptoms because they worried about potential SARS-CoV-2 infection. This hypothesis of delayed presentation is partly supported by an observed increase in out-of-hospital cardiac arrests [5] and overall mortality [6] during the COVID-19 pandemic.

In this issue of *Kardiologia Polska (Kardiol Pol, Polish Heart Journal)*, Jankowska-Sanetra and colleagues [7] present the results of a multi-institutional Polish registry including patients hospitalized for ACS from June to October 2020, following the first wave of the COVID-19 pandemic. The authors collected data from more than 4500 subjects and then compared them with those from patients hospitalized for ACS during the corresponding time frame in 2019 before the pandemic outbreak. The main objective of their survey was to assess the impact of the first lockdown on ACS incidence, modality of treatment, and outcomes. Rather than focusing on the first COVID-19 wave, the authors specifically addressed the period immediately after to provide a picture of the population's health status following the first lockdown. As compared to June-October 2019, a higher number of ACS hospitalizations (mainly ST-segment elevation myocardial infarction [STEMI] and unstable angina [UA]) in relation to the overall hospitalizations for invasive procedures was reported in the corresponding time frame of 2020 (57.9% ACS vs. 42.1% elective cases in 2020 and 52.9% ACS vs. 47.1% elective cases in 2019). In 2020, patients admitted for ACS had a worse cardiovascular risk profile with a higher prevalence of hypertension, diabetes mellitus, hyperlipidemia, and smoking habits. Moreover, procedural data showed that the percentage of percutaneous vs. surgical revascularizations increased following the first COVID-19 wave, and multivessel coronary disease was more often treated in a single rather than in multiple staged procedures.

The investigators should be congratulated for their effort, aiming to provide a clear picture of the health status of acute cardiac patients immediately after the first COVID-19 wave. The focus on this specific time frame provides readers with new insights into the impact of the COVID-19 pandemic on cardiac patients. In particular, the following topics are addressed: (1) the influence of the first lockdown on lifestyle habits; (2) the reasons for hospital admissions following the first COVID-19 wave; and (3) the temporal changes of ACS management during the COVID waves.

First, as evidenced by the higher prevalence of cardiovascular risk factors as compared to the non-pandemic period, the lockdown negatively influenced lifestyle habits. This hypothesis is in line with previous studies, reporting a diffuse worsening of lifestyle behaviors during the COVID-19 pandemic with a concomitant increase in stress, sedentariness, smoking, and alcohol consumption [8, 9]. A concurrent decline in cardiovascular risk factor control, such as hypertension and diabetes, has been previously reported [10, 11].

Second, the authors describe an increased hospitalization rate for ACS, mainly explained by a higher incidence of UA and STEMI cases in the post-lockdown period as compared to the previous non-pandemic year. These data should be interpreted in light of several considerations. The above-mentioned worsening of risk factor control, the under- or misdiagnosed cardiac conditions during the first wave, and the increased ED admissions due to subsiding fear of contagion may have contributed to these findings. Interestingly, the overall number of ACS patients remained stable as compared to the previous year (2620 vs. 2801 in 2020 and 2019, respectively). This finding is in line with a large epidemiological UK study reporting a partial reversion of ACS reduction following the first pandemic wave in 2020 [12]. Taken together these data suggest that the fear of COVID-19, in addition to the disease itself, negatively impacted clinical conditions of cardiac patients and that the pandemic effect on the healthcare system and reduction of elective procedures continued beyond the first lockdown.

Finally, this article provides important insights into the management of ACS during the COVID-19 pandemic. The higher incidence of STEMI led to a higher number of primary PCIs, whereas the stable ACS rate (similar to the previous years) indicates that there was a marked preference for PCI over cardiac surgery. As suggested by previous research, this might be explained by the policy of healthcare systems to optimize resources [12, 13], by Heart Teams' concerns about the risk of patients contracting the infection in post-acute care facilities [14], and by the extreme shortage of beds in intensive care units [15].

The findings by Jankowska-Sanetra et al. [7] are intriguing and lead one to wonder whether the subsequent pandemic waves had a similar effect on cardiac patients, or whether a better disease understanding along with improved resource allocation led to different outcomes.

Article information

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Cardiac resynchronization in heart failure: Recent advances and their practical implications

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ABSTRACT

Cardiac resynchronisation (CRT) improves survival and reduces heart failure hospitalisations, in symptomatic patients with heart failure (HF) with reduced ejection fraction with wide QRS despite guidelines indicated medical therapy. In patients with mild HF symptoms (New York Heart Association [NYHA], class II) CRT delays or reverses disease progression. Still, CRT is largely underused. The results of CRT Survey II indicates wide adoption of class I indications in European Society of Cardiology guidelines but with important national differences. As an example more patients in Poland had ischemic HF etiology and in NYHA III than in the overall CRT cohort. Similar patterns were seen in other countries suggesting that some patients such as those in NYHA II and with non-ischemic aetiology may be especially underserved by CRT. But the Survey results also shows wide use in areas with week scientific evidence such in atrial fibrillation (AF) and when upgrading from ongoing implantable cardioverter defibrillator or right ventricular pacing to CRT. This practise may imply the belief of the physcian than CRT may but also highlights the need of randomised studies to elucidate CRT effects in such patients. Besides, gaps of evidence the review further discusses reasons for obstacles for CRT implementation and the challenges with the traditional responder definition which may deter the clinician from offering CRT therapy. Finally, the importance of sex and body size for electrical selection criteria for CRT are discussed. A person with small body size and/or female sex may may derive CRT benefit at shorter QRS durations than a bigger individual indicating the need to shift to personalized medicine.

Key words: cardiac resynchronization therapy, chronic heart failure, implementation, indications, atrial fibrillation, sex-differences

INTRODUCTION

Cardiac resynchronization therapy (CRT) first introduced in the late 1990s has been shown to improve survival, reduce heart failure hospitalizations, improve exercise tolerance, and quality of life in patients with heart failure (HF) with reduced ejection fraction (HFrEF) who remain symptomatic and with wide QRS despite guidelines indicating medical therapy (GMDT) in pivotal trials [1–7]. In later years there have been many breakthroughs in HF medication reflected in recent guidelines, with the SGLT2 inhibitors indicated in patients with HFrEF. In addition, the sequential approach to initiating HF drugs has been recommended to be replaced by initiation of all four guidelines-indicated drugs within the first month of treatment. Moreover, most of these drugs also reduce the risk of sudden cardiac death (SCD), which makes the decision to provide a primary preventive defibrillator in CRT (CRT-D) especially challenging.

Guidelines state that CRT is indicated in a subset of HFrEF patients when HF medication is insufficient [8]. CRT is indicated in patients with left bundle branch block (LBBB) and wide QRS, with a class I level of evidence A for QRS width ≥150 ms and with a class IIa for QRS width 130–149 ms [8]. For patients without LBBB, the recommendations are class IIa or IIb depending on QRS width. Importantly, CRT is contraindicated in QRS width <130 ms [9] because normal or near normal conduction and activation of the ventricles are always superior to those induced by pacing, including biventricular pacing.

CRT is effective in symptomatic HF patients, meaning New York Heart Association

(NYHA) class II–IV [1–7]. One of the main mechanisms of action is left ventricular (LV) reverse remodeling. This process starts immediately after CRT is turned on [10] and further evolves over 2 years [11]. In REVERSE, we could also demonstrate sustained LV reverse remodeling over 5 years [12] and linked it to low mortality and morbidity. This means that CRT both reverses remodeling and delays disease progression at least when given in early disease states. But do patients get access to this life-saving therapy?

CRT PRACTICE ACROSS ESC COUNTRIES: EHRA HFA CRT SURVEY I AND II

Registry studies have shown that up to two-thirds of eligible patients are not treated with CRT [13], and CRT care is often suboptimal, which reduces treatment effects. We know from the European Heart Rhythm Association (EhrA) white book that implementation of CRT is low with a median implantation rate of 86/milion [13, 14]. CRT Survey II therefore aimed at studying indications and practice of CRT across European Society of Cardiology (ESC) countries to identify obstacles to device implementation and to enhance therapy use [15]. It included 11 088 CRT recipients (*de novo* or upgrades) from 42 ESC member countries. Poland was the greatest contributor with 1241 patients. The most common reason for CRT in this Survey was moderate HF, with 58% of CRT implantations performed in patients in NYHA class III. In addition, 48% had an HF hospitalization within the last year as a marker of disease severity. Importantly, even in countries like Germany with the highest overall implantation rate in all ESC countries, the proportion of CRT in NYHA II was low, suggesting overall under-implementation of therapy and in particular in NYHA class II for which CRT might be of particular value in delaying disease progression.

CRT practice in CRT Survey II reflected the ESC guidelines. However, weaker recommendations were also used. For example, 26% of CRT therapy was given in atrial fibrillation (AF) patients, and upgrades from ongoing implantable cardioverter defibrillator (ICD) or right ventricular (RV) pacing constituted 28%, particularly in countries with a long tradition of CRT therapy.

In the Survey, more patients in Poland had ischemic HF etiology than in the overall CRT cohort, and there were more patients in NYHA class III and with more comorbidities [16].

CRT IN PATIENTS IN NEED OF RV PACING

It is well-known that patients paced in the RV $\geq$20% and with a normal intrinsic conduction risk developing LV dysfunction and, in time, heart failure as evidenced in the DAVID [17] and MOST trials [18], which is both avoidable and unacceptable. The BLOCK-HF study showed that CRT therapy in such patients is superior to RV pacing for reducing mortality and HF hospitalizations and improving LV function [19] and thus is preferable in patients in need of RV pacing. Reflecting this fact, 18% of CRT was given to patients in need of pacing in CRT Survey II [15]. The guidelines' recommendation was, however, published after Survey II was planned.

There is a reason to believe that this indication is not widely adopted although it has a class I level A recommendation in the current guidelines [8]. It may be because many patients have intermittent high-degree atrioventricular (AV) block and most DDD-pacemakers have algorithms adjusting AV delay to allow intrinsic conduction and thus minimize the level of RV pacing. But this approach will require careful monitoring and documentation since the extent of RV pacing, as well as LV function, may change over time. In the future, the risk of RV pacing-induced HF may decline due to the potential greater use of leadless pacing or His pacing when such techniques are available and feasible.

But currently and according to the 2021 ESC and EHRA pacing and CRT guidelines, His pacing should be considered when placement of a coronary sinus lead to achieve CRT is not possible [8]. The guidelines also stress that lead problems, such as stimulation threshold elevations in His bundle or lead dislodgement, may arise and state that an RV backup pacing lead should be implanted in pacemaker-dependent pacing [8].

CRT IN ATRIAL FIBRILLATION

Atrial fibrillation accompanies heart failure, and its prevalence increases in patients with more severe HF symptoms meaning that 10%–50% of those with HFrEF have AF. Yet the efficacy of CRT in AF patients has not been studied in CRT randomized controlled studies, and the results of small randomised studies (MUSTIC-AF) and observational studies are still conflicting. The MUSTIC-AF was a small crossover study of HF patients with permanent AF. Comparing RV to CRT pacing, the study showed improved exercise tolerance but only modest LV remodeling with CRT compared to RV pacing [20]. In the much larger RAFT trial, there were 229 HF patients with permanent AF randomized to CRT-ICD or ICD alone [7]. In a post hoc analysis, no benefit in the combined primary endpoint of all-cause mortality and HF hospitalizations was shown in AF patients, but the trial was not powered to show clear treatment effects in patients with AF. The results of a meta-analysis of retrospective studies suggest CRT benefits may be attenuated in patients with a history of AF [21]. Although AF has been an exclusion criterion in many CRT recipients, many study patients had a history of AF when randomized. In a post hoc analysis of the COMPANION trial, the benefits of CRT were compared between patients with sinus rhythm and those with a history of AF [22]. Again, there was no benefit of CRT in patients with a history of AF. One probable contributing factor to the inferiority or no benefit of CRT in AF patients is the lack of delivery of therapy since intrinsic conduction overrides biventricular stimulation, for example, during exercise. AV junction ablation is recommended to ascertain delivery of biventricular pacing in such patients [8, 23].

Despite a clear lack of evidence, CRT Survey II shows that as much as 1 in 4 of those who received CRT therapy were AF patients, which shows that many cardiologists are convinced that CRT is beneficial despite the lack of evidence. In conclusion, there is a clear need for a randomized study in AF patients.

UPGRADING

Patients who develop HF and LVEF <35% during treatment with an ICD or an RV-based pacemaker and who have RV pacing ≥20% of the time should be considered for upgrading to CRT (level of evidence IIa B) based on the current guidelines [8], but the scientific evidence for this recommendation is insufficient. From CRT Survey II, we know that upgrading is common across ESC countries with no apparent excess perioperative risk in conjunction with the implantation procedures compared to *de novo* CRT implantation despite older age in upgraded patients [24].

The Budapest CRT upgrade study [25] is a prospective randomized trial that is ongoing. It compares upgrades from RV pacing or ICD to CRT-D or CRT-P in patients who had low LVEF (150 ms) and ≥20% RV pacing without having intrinsic LBBB, RV dilatation (RV diameter >50 mm), severe valve impairment, or severe renal impairment (>200 µmol/l). The baseline characteristics have been published [26] and show that patients are in their early 70s and with multiple comorbidities. Results will be presented very soon and will show the outcomes of CRT upgrade with respect to all-cause mortality, HF events, and echocardiographic response. The results may contribute to a more precise definition and extension of the current guidelines for CRT upgrades. The study is unique and will hopefully elucidate the value of upgrading to CRT for better? outcomes.

CRT RESPONSE

Response to therapy traditionally has been categorized as improved, unchanged, or worsened. Indeed, in HF trials, Packer introduced a combined endpoint for HF trials, and this endpoint has been extensively used in CRT trials. It consists of a combination of mortality, HF hospitalization, NYHA class, and patients' global assessment, defining patients as improved, unchanged, or worsened [27].

In oncology, partial remission has long been recognized as an acceptable response to therapy. In contrast, cardiology has only accepted improvements as a response to CRT even though HF is a chronic disease just like many cancers (Figure 1). One of the major challenges is thus that as much as 30%–40% of patients are said not to "respond" to CRT, which encompasses both cases unchanged or worsened by CRT. Such a high non-response rate may well deter physicians from referring patients for CRT, and it may well contribute to under-implementation of CRT together with the high upfront cost of the device and the fear of complications. Requirements for individual response are absent in HF drug therapy, and thus many patients do not perceive a difference when additional guidelines indicated medications should be given in addition to the existing ones. CRT is always given on top of HF medication, but still a "response" — meaning improved disease state — is required for a physician to classify the outcome benefits.

In CRT studies, the response is defined by a 6- or 12-month reduction in LV end-systolic volume index and NYHA class or a combination of the two. But there are many reasons to believe this definition may be outdated. There is emerging evidence that an unchanged condition (often called stabilization or non-progression) is also positive for the patient. For example, it has long been known that CRT in patients with ischemic HF etiology improves outcomes despite the limited extent of reverse remodeling [10].

REVERSE was a multinational randomized controlled trials (RCT) comparing CRT to non-CRT in NYHA class II HF patients. In the trial design, left ventricular end-systolic volume index (LVEVSI) change was the secondary powered endpoint, and the primary endpoint was the composite Packer's endpoint. Packer's combined endpoint was only significant after 2 years of results [10] but reached only borderline significance after one year [7] reflecting mild disease state in randomized patients.

In a subsequent substudy based on patients assigned to CRT at randomization, we looked at the impact of these two endpoints, both evaluated within the first year, and compared 5-year mortality in patients judged as worsened to those judged as stabilized (unchanged) or improved. A similar probability of death in those stabilized or improved was found (Figure 2). In contrast, patients who worsened had significantly worse prognoses [28–29]. The conclusion is twofold. Firstly, the lack of early improvement in LVESVi or clinical improvement does not preclude subsequent outcome benefits. Secondly and importantly, patients who deteriorate during CRT need to be considered for advanced therapies [30].

WOMEN AND BODY SIZE

There is reason to believe that women are undertreated with CRT and women constituted 25% of CRT implantations in CRT Survey II [15]. Women more often have LBBB [31] than men and dilated cardiomyopathy, both linked to CRT benefits.

But women also have smaller QRS width than men and therefore may not fulfill guidelines Class I recommendations for CRT [8]. In addition, CRT studies are based on 25% females as study patients. Women are said to have been underrepresented in CRT trials, and not fulfilling the QRS width criteria may be one reason, but another is that women less often have HFrEF and more often have HF with preserved ejection fraction (HFpEF) [32].

Both differences in QRS widths but also in body size and height may distinguish women and men more likely to respond to CRT. In a pooled metanalysis based on 4076 patients in 2 RCTs, women [33] benefited from CRT-D more than men. In patients with LBBB and QRS of

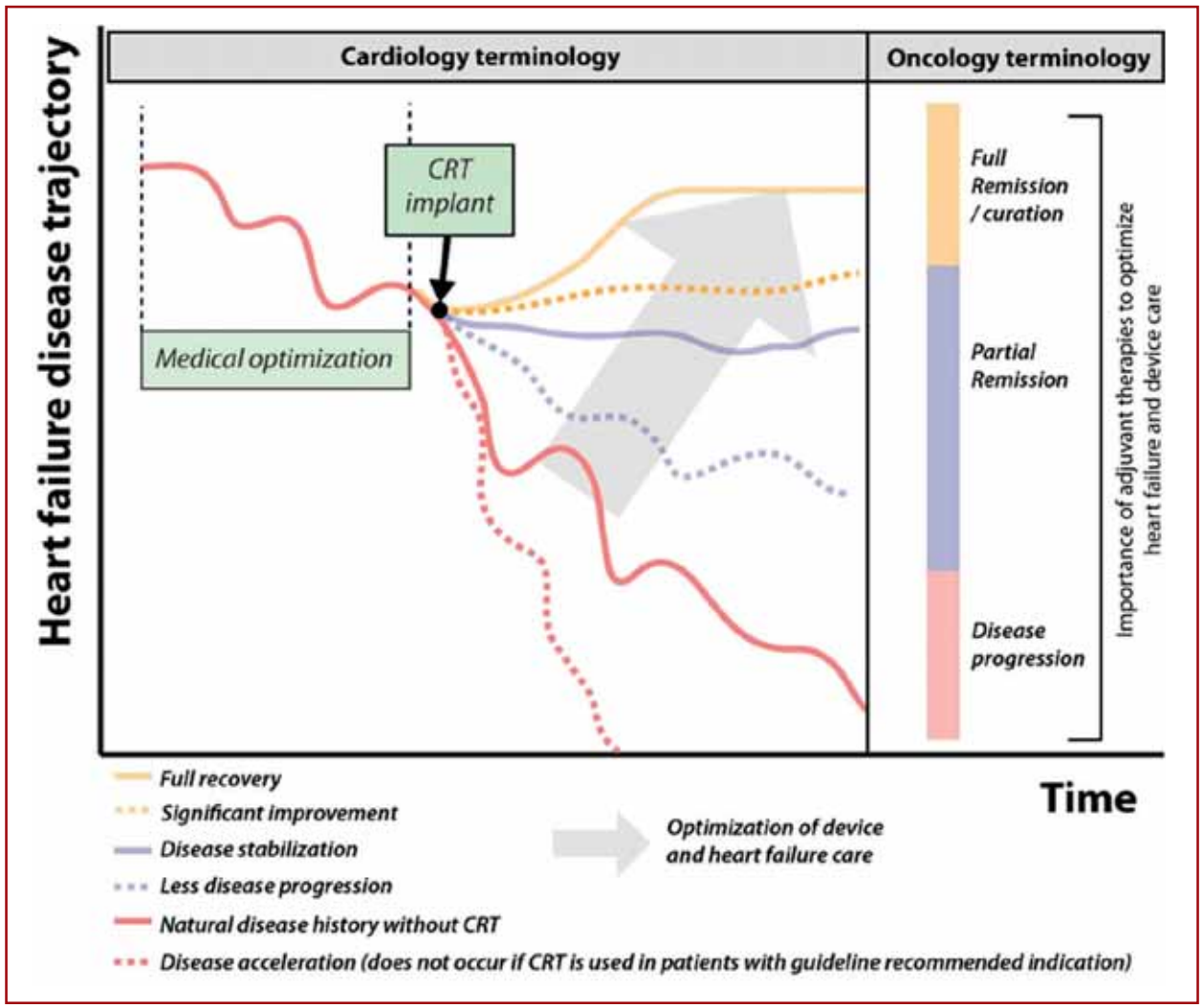

Figure 1. Role of cardiac resynchronization therapy (CRT) in disease modification of the heart failure trajectory

Reproduced with permission, from: Mullens W, et al. Optimized implementation of cardiac resynchronization therapy: a call for action or referral and optimization of care. Eur J Heart Fail. 2020; 22(12): 2349–2369, doi: 10.1002/ejhf.2046, indexed in Pubmed: 33136300

Abbreviations: CRT, cardiac resynchronisation therapy

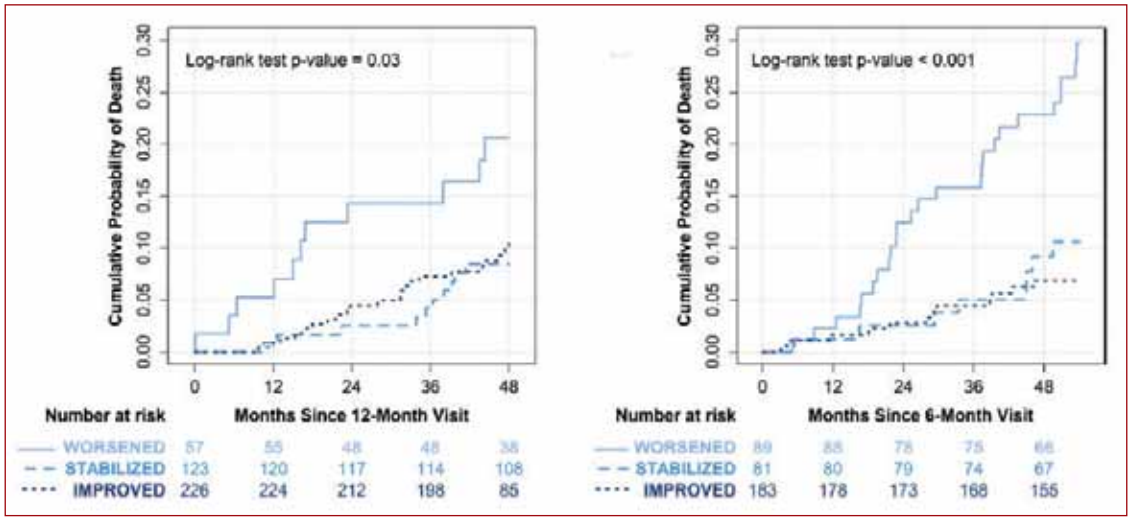

Figure 2. Long-term mortality in patients assigned to CRT in the REVERSE study according to one-year response: worsened, stabilized, or improved

Reproduced with permission, from: Gold MR, et al. Redefining the classifications of response to cardiac resynchronization therapy. JACC Clin Electrophysiol. 2021; 7(7): 871–880, doi: 10.1016/j.jacep.2020.11.010, indexed in Pubmed: 33640347

130–149 ms (for which current guidelines have class IIa recommendation [8]), only women benefited from CRT. Women had a 76% reduction in HF or death (absolute CRT-D to ICD difference, 23%; hazard ratio [HR], 0.24; 95% confidence interval [CI], 0.11–0.53; *P* <0.001) and a 76% reduction in death alone (absolute difference 9%; HR, 0.24; 95% CI, 0.06–0.89; *P* = 0.03). Both sexes with LBBB benefited at QRS of ≥150 ms. What could be the reason? Firstly, the relationship between QRS width and CRT benefit for outcomes has been clearly demonstrated in another individual case-based meta-analysis of 5 RCTs [34]. Secondly, when sex differences were analyzed in a subsequent publication, height was shown to be more important for response than sex per se with a greater CRT response in shorter persons. Thus, when height for men was divided into tertiles, the shorter men (median 167 cm) responded better to CRT and those with smaller QRS widths just like women [35]. Taller men only benefited at QRS widths >150 ms. A later case-based meta-analysis confirmed a greater CRT response with smaller height, body weight, and body surface area (BSA) (better effects for small/low or medium rather than tall) (Figure 3) [36].

Finally, there may be a reluctance to give women CRT since in CRT Survey II, they had a higher procedural complication rate related to vascular access as evidenced by pneumothorax (1.4%), coronary sinus dissection (2.1%), and pericardial tamponade (0.3%). The probable reason is the smaller dimensions of vessels in women compared to men [37]. In conclusion: we need to move into precision medicine taking not only sex but body size and ethnicity into account in clinical decision-making for CRT.

CHOICE OF CRT-D OR CRT-P IN PRIMARY PREVENTION OF SUDDEN CARDIAC DEATH

With the evolution of HF-modifying medication and CRT, the relative risk of sudden cardiac death has been reduced by more than 40% [38]. Not all sudden death is due to ventricular tachyarrhythmia and is thus preventable with ICD. Moreover, with each added guideline indicating HF medication, the risk of both total mortality and SCD decreased [39]. CRT per se also reduces the risk of sudden cardiac death [40]. Following the negative results of the DANISH trial [41] comparing ICD with or without CRT with no ICD, the challenges to deciding on CRT-P and CRT-D have increased. Preventive models to evaluate the risk of SCD against that of total mortality have been introduced, for example, with an updated version of the Seattle risk model which balances the risk of SCD vs. non-SCD to help in decision-making [42]. The 2021 ESC and EHRA guidelines on pacing and CRT also include such help and take the presence of myocardial scar tissue into account [8]. Ultimately, there is a need for a randomized study, and the RESET CRT study that randomizes patients to CRT-P to CRT-D is ongoing. However, a published prelude to the RESET CRT study reported no survival benefit in CRT-D patients over CRT-P patients after entropy balancing and age adjustment [43].

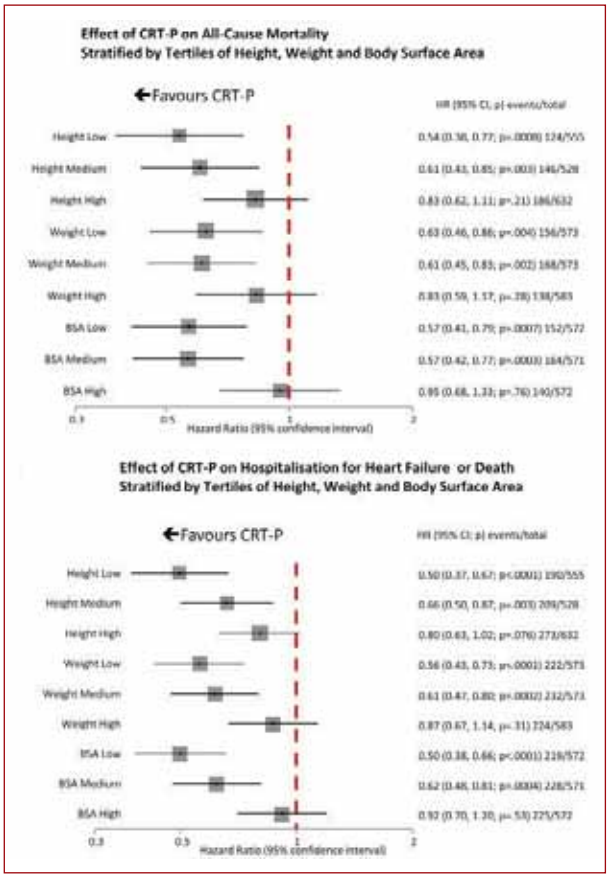

Figure 3. Effect of cardiac resynchronization therapy (CRT) on all-cause mortality and heart failure hospitalizations stratified by height, weight, and body surface area (BSA) tertiles

Reproduced with permission, from: Cleland JWG, et al. The effect of cardiac resynchronization without defibrillator on morbidity and mortality. Eur J Heart Fail. 2022; 24(6): 1080–1090, doi: 10.1002/ejhf.2524

Abbreviations: BSA, body surface area; CRT-P, cardiac resynchronization therapy pacemaker

Ongoing projects to build models to predict risk for SCD after acute myocardial infarction such as PROFID will determine the value of clinical prediction models in neural networks (profid-project.eu).

HF THERAPY IMPLEMENTATION

But the greatest challenge is to properly ensure that HF medications are given to HFrEF patients. Beta-blockers, angiotensin receptor-neprilysin inhibitor (ARNI) and MRA all reduce the risk of sudden cardiac death as does CRT through reverse remodeling [39, 40, 44]. SGLT2i also reduces the risk of sudden cardiac death [45]. Therefore, a swift introduction of these disease-modifying drugs is needed and thorough evaluation of clinical findings and echocardiography before deciding on device implantation [46].

This new more rapid approach will require good organization of HF care and deciding whether the patient is a potential candidate for CRT ± ICD. If the patient improves to an extent such that CRT or ICD are unnecessary, it is always easier to cancel plans for device therapy than

the reverse. In short, HF care, including device therapy, heavily depends on multidisciplinary HF teams with a care plan for each patient with rapid revision according to the disease state of the individual. Results from the Swedish HF National registry show that therapy implementation including CRT is increased in such care, which, in turn, is linked to improved outcomes [47, 48].

In conclusion: after ascertaining optimal medical therapy and shared decision-making with the patient [8], as suggested in the ESC EHRA pacing and CRT guidelines, life expectancy, and comorbid factors are the best premises for decision-making we have at present.

Future implications

Except for the challenges in therapy implementation, new pacing techniques such as physiologic pacing will become increasingly important. However, the scientific evidence is not sufficient for guidelines [8] to make firm recommendations for His pacing unless when conventional LV lead placement is not possible. Both His pacing and left bundle pacing are currently studied in many ongoing RCTs. Conduction system pacing appears to prevent adverse effects of chronic RV pacing, and early data suggest potential benefits in CRT-indicated patients. Randomized clinical trials to evaluate the role of His bundle or left bundle area pacing as an alternative to RV pacing or in CRT-indicated patients are needed

Article information

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Prevalence of atrial fibrillation in the 65 or over Polish population. Report of cross-sectional NOMED-AF study

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Editorial
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ABSTRACT

Background: Atrial fibrillation (AF) is the most common cardiac arrhythmia, characterized by an increased risk of thromboembolic complications that can be markedly reduced with anticoagulation. There is a paucity of studies assessing the total prevalence of AF in national populations.

Aims: To assess the nationwide prevalence of AF in a population of adults ≥65 years old and to determine the impact of duration of electrocardiogram (ECG) monitoring on the number of newly detected AF episodes.

Methods: The NOMED-AF study (ClinicalTrials.gov; NCT: 0324347) was a cross-sectional study performed on a nationally representative random sample of 3014 Polish citizens 65 years or older. Final estimates were adjusted to the national population. All participants underwent up to 30 days of continuous ECG monitoring. Total AF prevalence was diagnosed based on the patient's medical records or the presence of AF in ECG monitoring.

Results: The prevalence of AF in the Polish population ≥65 years was estimated as 19.2% (95% confidence interval [CI], 17.9%–20.6%). This included 4.1% (95% CI, 3.5%–4.8%) newly diagnosed cases and 15.1% (95% CI, 13.9%–16.3%) previously diagnosed cases and consisted of 10.8% (95% CI, 9.8%–11.9%) paroxysmal AF and 8.4% (95% CI, 7.5%–9.4%) persistent/permanent AF. The incidence of all paroxysmal AF events as a function of ECG monitoring duration increased from 1.9% (95% CI, 1.4%–2.6%) at 24 hours to 6.2% (95% CI, 5.3%–7.2%) at 4 weeks.

Conclusions: The prevalence of AF in elderly adults is higher than estimated based on medical records only. Four weeks of monitoring compared to 24-hour ECG Holter allow detection of 7-fold more cases of previously undiagnosed paroxysmal AF.

Key words: atrial fibrillation, long-term ECG monitoring, population prevalence, silent atrial fibrillation

WHAT'S NEW?

The true prevalence of atrial fibrillation in Poland in the elderly population is significantly higher than estimated based on medical records only. Systematic, populational long-term electrocardiogram monitoring for up to thirty days is feasible and increases the number of detected atrial fibrillation cases twice compared to 1-week monitoring.

INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia [1] characterized by an increased risk of thromboembolic complications, including ischemic stroke (IS). The risk of IS can be markedly reduced with anticoagulation. Nonetheless, approximately 16% of cryptogenic stroke cases are still related to AF [2] because AF often remains undiagnosed.

Despite tremendous interest in AF and its epidemiology during recent years, there is a paucity of studies directly assessing the total prevalence of AF in national populations, using representative methods and diagnostic approaches recommended by clinical guidelines.

Existing national estimates of the proportion and numbers of AF patients are derived from analyses of registry data and modeling studies rather than direct surveys [1, 3], often including only diagnosed cases of AF [4]. More detailed studies are available for selected subgroups such as post-stroke patients [5], subjects with implanted pacemakers or implantable cardioverter defibrillators [6], voluntary screening program participants [7], smartwatch users [8, 9], and local communities. While these estimates are often generalized to national populations, unproven assumptions of negligible selection bias make them less trustworthy. The published estimates for the same population differ from one another considerably.

Fewer data are available for the prevalence of undetected AF in an entire national population. This is important because these individuals represent a missed opportunity for stroke prevention. Previously unknown AF is a common finding in patients hospitalized with acute stroke. According to registry data, previously undetected AF was found in 8.1% of post-stroke patients in Sweden [10]. Even more cases are detected if patients' electrocardiogram (ECG) is monitored for longer than routine 24-hour Holter recording [11].

The main objectives of this article are (1) to assess the prevalence of AF in a nationally representative sample of Polish adults 65 years or older, including asymptomatic cases, using a clinical diagnostic approach based on current guidelines; and (2) to evaluate the impact of ECG monitoring duration on the number of newly detected paroxysmal cases of AF.

METHODS

The NOMED-AF is a cross-sectional study to estimate the prevalence of AF, including undetected AF, in the population of Polish citizens aged 65 years or older. The study was conducted from March 15, 2017 to March 10, 2018. It complied with the Declaration of Helsinki and was approved by the Local Bioethical Committee of the Silesian Medical Board (26/2015) and registered on ClinicalTrials.gov (NCT03243474). Details of the study design were published elsewhere [12].

Study sample

The sample consisted of 3014 randomly chosen individuals, representative of the general, noninstitutionalized Polish population aged 65 or older. The multistage, stratified, and clustered sampling procedure was used. Details of the sample selection procedure are provided in the Supplementary material. In short, the whole territory of the country was stratified into 59 geographical strata. Then, separately in each stratum, municipalities were sampled with the probability proportional to population size. In each municipality, one or more villages or streets were drawn. Finally, individual respondents were selected randomly. The sampling frame consisted of all individuals living in selected villages/streets, aged 65+, recorded in the PESEL database (national registry covering all Polish citizens). Similar numbers of men and women were selected in each age category (65–69, 70–74, 75–79, 80–84, 85–89, and 90+ years). This resulted in oversampling of older age groups. This was done to ensure that the size of the final subsample of the most aged subjects would be enough for separate analyses. The oversampling was corrected with weights to get population estimates at the statistical analysis stage.

For each of the 3000 participants, another 9 subjects living in the same cluster were drawn. These "spare" addresses were used in a predefined random order only if the address of the primarily chosen subject was incorrect or an individual refused to participate in the study.

Patients' inability to answer the questionnaire (i.e., because of dementia) did not exclude them from the study. In such cases, caregivers or close family members were asked to provide information. This was done to avoid selection bias towards the healthier part of the population. Patients with already diagnosed AF were included. The only exclusion criteria were the lack of the subject's consent or presence of factors preventing the study nurse from contacting an individual (extremely rare).

Data collection

A trained nurse interviewed each study participant at home using a standardized questionnaire. The questions relevant to the current analysis included previous diagnosis of AF, symptoms related to AF incidents, and existence of

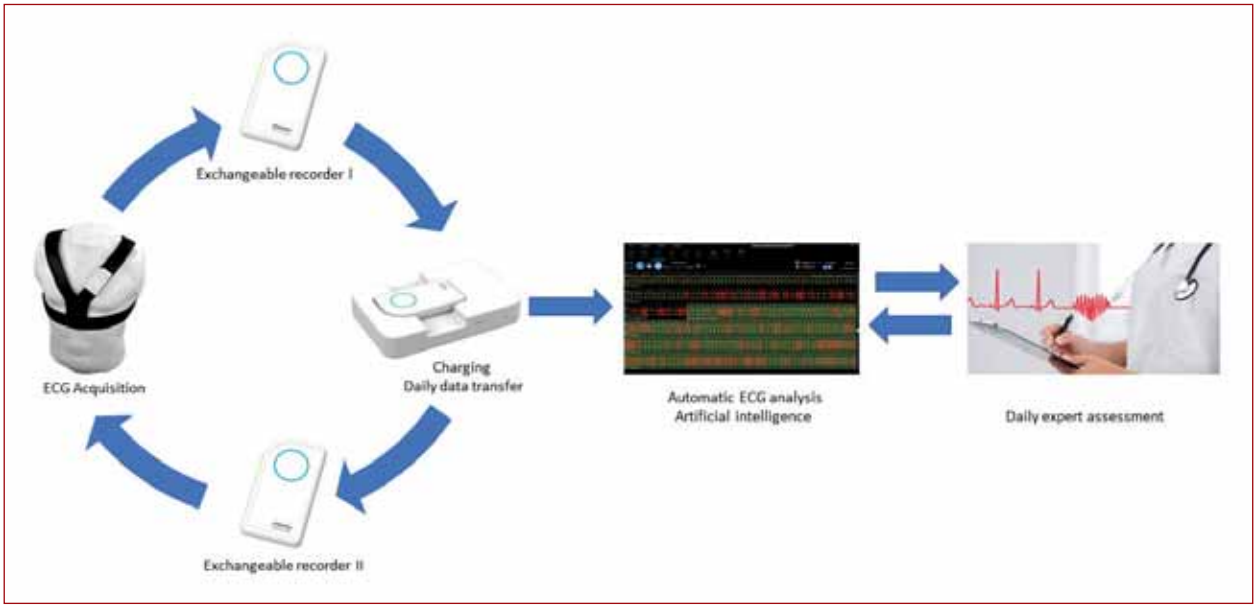

Figure 1. The scheme of the atrial fibrillation monitoring system used in the study
Abbreviations: ECG, electrocardiography

other cardiovascular diseases, diabetes, and chronic kidney disease. The nurse also collected data needed to calculate the CHA_2DS_2-VASc score.

Moreover, height and weight were measured using portable scales. Blood pressure was measured during two separate visits at home using validated automated oscillometric devices. Urine and fasting blood samples were collected and processed in the central laboratory.

Long-term ECG monitoring

Thirty-day, surface, 2-lead ECG recording was attempted in each study subject, including respondents with already diagnosed AF. Comarch Healthcare (Kraków, Poland) developed and manufactured a dedicated ECG monitoring system specifically for this study. The system consisted of a vest equipped with ECG leads, two exchangeable recorders, and a docking station allowing to charge recorders and transmit data. Another recorder was connected at the same time to the vest and recording. ECG data were transmitted to a central database using GSM technology (Figure 1).

The ECG recording was screened automatically for AF and atrial flutter episodes lasting longer than 30 seconds, using software developed and validated especially for the study. Episodes of atrial fibrillation/atrial flutter lasting longer than 30 seconds were automatically detected by AF detection algorithms of the analytical platform. Finally, each of the automatically detected episodes was reviewed by expert cardiologists.

Laboratory analyses

A trained nurse collected blood for N-terminal pro-B-type natriuretic peptide (NT-proBNP) measurements in the respondent's home into a lithium heparin tube. The collected sample was processed in a local laboratory within a maximum of four hours; the plasma was separated and then frozen at temperatures of –20° C and transported to the central laboratory in Gdańsk, Poland, on dry ice. NT-proBNP concentration was determined using the immune chemiluminescence method on the Immulite 2000 analyzer (Siemens Healthineers, Erlangen, Deutschland).

Outcomes

The presence of AF was established based on the patient's medical records assessed for all subjects by the trained study nurse on-site, confirmed by ECG record/monitoring (all participants had long-term ECG monitoring). The new AF cases (not previously detected) were established based on up to 30 days of surface ECG monitoring for episodes of AF lasting 30 seconds or longer. Newly diagnosed AF was defined as AF found in patients without previous history of this arrhythmia in available medical documentation. In this article, the term AF refers both to atrial fibrillation and atrial flutter.

Patients were diagnosed with paroxysmal AF if the duration of the recorded longest arrhythmia event was shorter than 7 days. All other cases were considered persistent/permanent. We analyzed both as one group because it is not always possible to distinguish between persistent and permanent AF using patients' medical documentation.

Silent AF (SAF) was defined as AF without typical clinical symptoms [13] (both previously known and newly diagnosed).

Definitions of exposure variables

The major exposure variable was the duration of ECG monitoring. The total number (including newly detected) cases of paroxysmal AF was reported.

Sex, age, and comorbidities were assessed by study questionnaires. Obesity was defined as a body mass in-

dex (BMI) value >25 kg/m^2, based on measured height and weight. Hypertension was diagnosed if, during two separate visits, the measured patient's systolic blood pressure was ≥140 mm Hg or diastolic blood pressure was ≥90 mm Hg or if the subjects were taking any antihypertensive agents during the preceding two weeks. Diabetes was defined as HbA1c ≥6.5% or the use of antidiabetic drugs. Chronic kidney disease was defined as an estimated glomerular filtration rate value <60 ml/min/1.73 m^2 (based on the Chronic Kidney Disease Epidemiology Collaboration formula) [14] or urine albumin/creatinine ratio ≥30 mg/g. The CHA_2DS_2-VASc score was calculated based on the mentioned above diagnoses and questionnaire data [15].

Statistical analysis

The statistical analysis was conducted using the IBM SPSS statistic v. 19 (IBM Corp, Armonk, NY, US).

The categorical variables were expressed as numbers and percentages, whereas continuous parameters were expressed as mean (standard deviation). The χ^2 and McNemar tests were used to compare categorical variables. Student's t-test was used to compare continuous variables. In the case of continuous variables, the normality of distribution was confirmed using the Kolmogorov-Smirnov test. For all comparisons, a two-tailed P <0.05 was considered significant.

Oversampling of elderly age groups was addressed using weights, which corrected the age and sex structure of the sample to the structure of the Polish population. Statistical analyses accounted for complex survey design. Prevalence and 95% confidence intervals (95% CI) were reported.

Finally, for each patient with paroxysmal AF, the number of hours of ECG monitoring before the first recorded AF event (lasting at least 30 seconds) was assessed. Based on these data, the relationship between the duration of ECG monitoring and the number of AF cases was assessed.

RESULTS

Among 7429 individuals eligible to participate, 3014 were interviewed, resulting in a response rate of 41%. This corresponds to a recent response rate of 44% in the National Health and Nutrition Survey (Continuous NHANES 2017–2018) among subjects aged 60 or older [16]. The reasons for non-participation are provided in Supplementary material, *Figure S1*. The complete characteristics of the study sample and corresponding estimates of the nationwide population are shown in Table 1. Compared to the group with no AF, individuals with newly diagnosed AF seemed to be less burdened by comorbidities included in the analysis than those with already diagnosed AF. Only stroke, chronic kidney disease, and abnormal levels of NT-proBNP were significantly more frequent in the population with newly diagnosed AF compared to the no-AF population.

ECG monitoring

Among the 3014 participants, an ECG signal was acquired in 2974 (98.7%). The mean duration of ECG acquisition was 21.9 (9.1) days, and 90.2% of the acquired ECG signals were eligible for analysis.

Based on medical history and long-term ECG monitoring, atrial fibrillation was confirmed or newly diagnosed in 680 participants (Table 1). Five hundred and fifteen subjects (75.7% of all with AF) experienced AF episodes registered by the ECG monitoring system and confirmed by the cardiologist during the monitoring period. In the remaining individuals, AF was documented based on medical history.

Prevalence of atrial fibrillation

After long-term monitoring, the prevalence of AF in a population of Polish citizens aged ≥65 years was 19.2% (95% CI, 17.9%–20.6%). This included 4.1% (95% CI, 3.5%–4.8%) of newly diagnosed cases and 15.1% (95% CI, 13.9%–16.3%) of previously diagnosed. This indicates that 21.4% (95% CI, 18.4%–24.7%) of all AF cases in the population remain undiagnosed. The percentage of newly diagnosed AF was somewhat lower in patients with obesity (19%), diabetes (16%), and much lower in patients with coronary heart disease (9%). Notably, 20% of AF cases in post-stroke patients were undiagnosed.

The most frequent type of AF was paroxysmal in 10.8% (95% CI, 9.8%–11.9%), followed by persistent/permanent in 8.4% (95% CI, 7.5%–9.4%). The prevalence of AF was higher in men than in women (23.3%; 95% CI, 21.2%–25.4% vs. 16.6%; 95% CI, 14.9%–18.3%; P <0.001) and was higher with increasing age, reaching 31.9% (95% CI, 28.3%–35.9%) among individuals aged ≥85 years (Table 2).

The prevalence of SAF was 3.5% (3.0%–4.1%), and the majority of the newly diagnosed cases were SAF (76%).

Effect of long-term ECG monitoring on AF detection

Among subjects without persistent or permanent AF, the percentage of individuals with recorded AF increased with the duration of monitoring. AF was detected in 1.9% (95% CI, 1.4%–2.6%) and 6.2% (95% CI, 5.3%–7.2%) if subjects were monitored for 24 hours and 4 weeks, respectively. This translates into 3.2-fold more AF cases detected and an absolute difference in diagnosed cases of 4.3% (95% CI, 3.6%–5.1%) in subjects monitored for 4 weeks vs. 24 hours.

The number of newly detected paroxysmal AF was 7-folded higher if patients were monitored for 4 weeks vs. 24 hours: 2.8% (95% CI, 2.3%–3.5%) vs. 0.4% (95% CI, 0.2%–0.6%), difference 2.5% (95% CI, 2.0%–3.1%). ECG monitoring for 1 week allowed for detection of 1.4% (95% CI, 1.1%–1.9%) of new cases of AF, which is 3.5-fold more than after 24-hour monitoring (Figure 2).

Table 1. Characteristics of the study sample and estimates for the population

Clinical characteristics	Total population	No AF	Newly diagnosed AF	Previously diagnosed AF	Total population	No AF	Newly diagnosed AF	Previously diagnosed AF	*P*-value (newly diagnosed vs. no AF)	*P*-value (previously diagnosed vs. no AF)
	Sample size, n (%)	Sample size, n (%)	Sample size, n (%)	Sample size, n (%)	Population estimate, % (95% CI)	Population estimate, % (95% CI)	Population estimate, % (95% CI)	Population estimate, % (95% CI)		
Male sex	1535 (50.9)	1122 (48.1)	93 (66.4)	320 (59.3)	39.3 (37.7–41)	37.3 (35.5–39.2)	53.9 (45.7–61.9)	45.9 (41.8–50.2)	<0.001	<0.001
Female sex	1479 (49.1)	1212 (51.9)	47 (33.6)	220 (40.7)	60.7 (59.0–62.3)	62.7 (60.8–64.5)	46.1 (38.1–54.3)	54.1 (49.8–58.2)		
Age group, years										
65–74	1204 (39.9)	1035 (44.3)	34 (24.3)	135 (25)	55.8 (54.1–57.5)	59.8 (57.9–61.6)	36.2 (28.4–44.8)	39.8 (35.5–44.2)		
75–84	1114 (37)	819 (35.1)	60 (42.9)	235 (43.5)	31.1 (29.6–32.6)	29.2 (27.6–30.9)	39.3 (31.8–47.3)	39.2 (35.1–43.4)	<0.001	<0.001
≥85	696 (23.1)	480 (20.6)	46 (32.9)	170 (31.5)	13.1 (12.4–13.8)	10.2 (11.9–100)	18.6 (31.6–100)	21 (18.3–24.1)		
Comorbidities										
Stroke	366 (12.2)	246 (10.5)	22 (15.7)	98 (18.1)	10.8 (9.8–11.9)	9.6 (8.5–10.9)	15 (10.9–20.2)	16.1 (13.5–19)	0.007	<0.001
Coronary heart disease	666 (22.3)	444 (19)	20 (14.3)	202 (37.4)	20.1 (18.7–21.7)	17.6 (16.2–19.2)	12.3 (8.1–18.3)	35.8 (31.3–40.5)	0.08	<0.001
Hypertension	2433 (81.2)	1856 (79.5)	114 (81.4)	463 (85.7)	80.9 (79.4–82.2)	79.4 (77.7–81)	81.5 (74.1–87.2)	88.6 (85.6–91)	0.55	<0.001
Obesity	923 (31.2)	686 (29.4)	47 (33.6)	337 (62.4)	33.1 (31.4–34.9)	31.5 (29.6–33.6)	34.5 (27.3–42.4)	41.1 (36.6–45.7)	0.46	<0.001
Diabetes	881 (29.2)	628 (26.9)	44 (31.4)	331 (61.3)	28.2 (26.6–29.8)	26.2 (24.4–28)	28.1 (22.1–34.9)	39.2 (35–43.5)	0.57	<0.001
Chronic kidney disease	1005 (34.4)	695 (29.8)	62 (44.3)	270 (50)	27.8 (26.3–29.4)	24.7 (23–26.4)	35.6 (28.6–43.2)	42.8 (38.4–47.2)	0.002	<0.001
Heart failure	673 (22.3)	396 (17)	24 (17.1)	286 (53)	18.3 (17.0–19.8)	13.7 (12.4–15.1)	13.7 (9–20.5)	44.4 (39.8–49.1)	0. 99	<0.001
NT-pro BNP >125 ng/ml	2288 (75.9)	1690 (72.4)	117 (83.6)	481 (89.1)	73.4 (71.6–75.1)	70.1 (68–72.1)	80.8 (73.5–86.5)	89.1 (85.4–91.9)	0. 006	<0.001
CHA_2DS_2-VASc, mean (SD)	4.0 (1.56)	3.9 (1.50)	4.0 (1.74)	4.8 (1.55)	3.9 (1.55)	3.7 (2.66–3.77)	3.9 (3.62–4.17)	4.7 (4.55–4.84)	0.18	<0.001

Abbreviations: AF, atrial fibrillation; CI, confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation

There were no statistically significant differences in demographic and clinical characteristics (including age, sex, comorbidities, and CHA_2DS_2-VASc score) between individuals with newly diagnosed paroxysmal AF after one week vs. 4 weeks of monitoring (Table 3).

DISCUSSION

The main findings of our study are as follows: (1) almost one-fifth of Polish citizens aged ≥65 years suffer from atrial fibrillation; (2) the prevalence of AF in this population based on medical history alone underestimates the actual value by more than 20%; (3) the number of newly diagnosed cases of paroxysmal AF is six-fold higher if patients are monitored for 30 days vs. standard 24 hours.

For most cardiovascular risk factors (i.e., hypertension, hypercholesterolemia, obesity, diabetes, etc.), country-level prevalence estimates are derived from nationally representative surveys [17, 18]. However, knowledge about the prevalence of AF at a population level is incomplete, derived from generalized estimates of registry data, local community samples, and modeling studies. Unfortunately, these designs are potentially more susceptible to both selection and information bias than studies utilizing population-representative random samples. For example, registry-based studies do not include undiagnosed disease cases and may ignore unknown fractions of unreported cases. Population-based cohort studies or clinical studies usually tend to exclude subjects with immobilizing comorbidities or dementia. As these conditions are associated with a higher probability of AF, excluding these patients may result in an underestimated prevalence of AF when their results are generalized to the entire population. Recent studies of smartphone users like the Apple Heart Study [8] are also not designed to assess the prevalence of AF in the general population because they include only selected participants (smartphone users, volunteers).

This leads to equivocal estimates of AF prevalence. For example, the data analysis derived from the ATRIA study estimated the total prevalence of diagnosed AF in a cohort of large northern California health maintenance group organizations as 3.8% in adults older than 60 years. These estimates, considered representative of the California state population, were later used to project the expected future prevalence of AF in the United States [4]. In contrast, Turakhia et al. [3], using commercial and Medicare administrative claims databases, estimated the prevalence of

Table 2. Estimates of the prevalence of all AF and previously diagnosed AF in 65+ Polish population by sex, age, existing comorbidities, and CHA_2DS_2-VASc score. Point estimates and 95% CI. *P*-value by the McNemar test for the difference between all and previously diagnosed AF cases. Thirty days of ECG monitoring significantly increased estimates of AF prevalence in the whole 65+ population and analyzed subgroups

Subgroup % (95% CI)	Total			Paroxysmal			Persistent or permanent		
	All	Previously diagnosed	*P*-value	All	Previously diagnosed	*P*-value	All	Previously diagnosed	*P*-value
All	19.2 (17.9–20.6)	15.1 (13.9–16.3)	<0.001	10.8 (9.8–11.9)	8.1 (7.2–9.1)	<0.001	8.4 (7.5–9.4)	7.0 (6.2–7.9)	<0.001
Male sex	23.3 (21.2–25.4)	17.6 (15.8–19.6)	<0.001	13.1 (11.4–14.9)	9.6 (8.1–11.2)	<0.001	10.2 (8.8–11.8)	8.1 (6.8–9.5)	<0.001
Female sex	16.6 (14.9–18.3)	13.4 (12.0–15.0)	<0.001	9.3 (8–10.8)	7.1 (6–8.4)	<0.001	7.2 (6.1–8.6)	6.3 (5.3–7.6)	<0.001
Age group, years									
65–74	13.4 (11.9–15.1)	10.7 (9.4–12.3)	<0.001	8.6 (7.3–10.1)	6.8 (5.6–8.2)	<0.001	4.8 (3.8–6.1)	4.0 (3.1–5.1)	<0.001
75–84	24.2 (21.7–26.8)	19 (16.8–21.5)	<0.001	13.2 (11.2–15.3)	10.0 (8.3–11.9)	<0.001	11 (9.4–12.9)	9.1 (7.5–10.8)	<0.001
≥85	31.9 (28.3–35.9)	24.2 (21.1–27.6)	<0.001	14.4 (11.8–17.3)	9.1 (7.2–11.4)	<0.001	17.6 (14.5–21.1)	15.2 (12.3–18.5)	<0.001
Comorbidities									
Stroke	28.1 (24.3–32.3)	22.4 (18.9–26.4)	<0.001	12.4 (9.8–15.5)	9.7 (7.4–12.6)	<0.001	15.7 (12.8–19.1)	12.7 (10.1–16)	<0.001
Coronary heart disease	29.2 (25.9–32.7)	26.6 (23.4–30.1)	<0.001	14.8 (12.2–17.9)	13.3 (10.8–16.3)	<0.001	14.4 (12–17.2)	13.3 (11–16.1)	<0.001
Hypertension	20.6 (19.2–22.2)	16.5 (15.1–17.9)	<0.001	11.9 (10.7–13.2)	8.9 (7.9–10.1)	<0.001	8.8 (7.8–9.9)	7.6 (6.6–8.6)	<0.001
Obesity	22.9 (20.3–25.7)	18.6 (16.2–21.3)	<0.001	11.8 (9.7–14.2)	8.9 (7–11.2)	<0.001	11.1 (9.4–13.2)	9.7 (8.0–11.6)	<0.001
Diabetes	25.0 (22.5–27.8)	21.0 (18.6–23.5)	<0.001	12.9 (11–15)	10.7 (8.9–12.6)	<0.001	12.2 (10.3–14.3)	10.3 (8.6–12.3)	<0.001
Chronic kidney disease	28.2 (25.2–31.4)	22.9 (20.1–26)	<0.001	13.5 (11.4–16.0)	10.1 (8.2-12.4)	<0.001	14.7 (12.6–17.1)	12.8 (10.8–15.1)	<0.001
CHA_2DS_2-VASc, mean (SD)	4.5 (1.70)	4.7 (1.63)	0.07	4.3 (1.66)	4.5 (1.65)	0.13	4.8 (1.73)	4.9 (1.59)	0.35

Abbreviations: see Figure 1 and Table 1

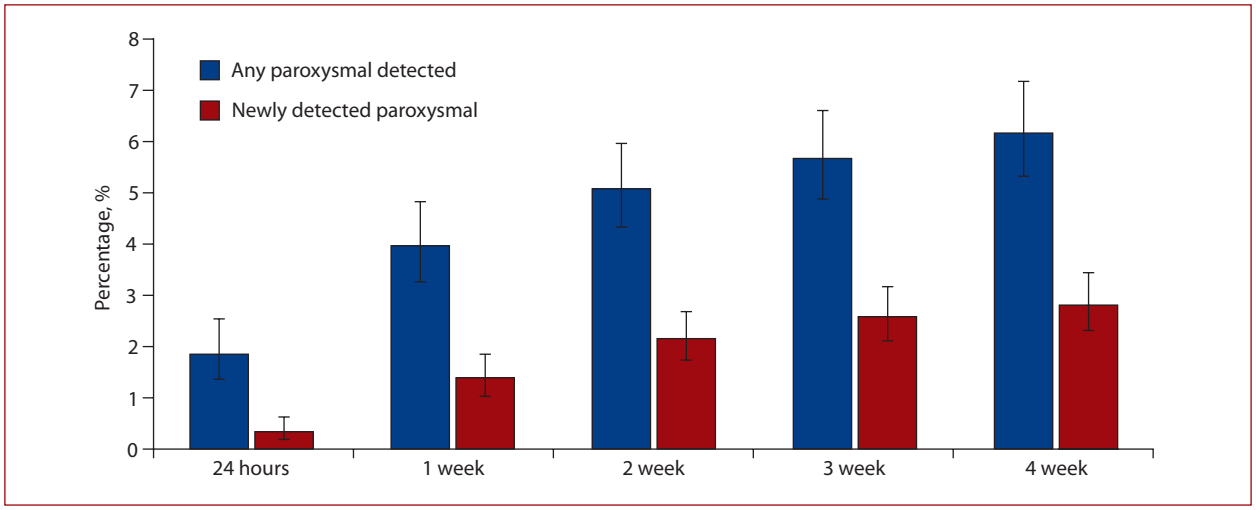

Figure 2. The prevalence (± 95% CI) of paroxysmal AF detected by long term ECG monitoring (total and newly detected) in Polish population ≥65 years as function of ECG monitoring duration. Detected prevalence after 4 weeks of monitoring was significantly higher than detected in 24 hours, 1 week, 2 weeks and 3 weeks in case of either any paroxysmal AF ($P<0.001$) or newly detected paroxysmal AF ($P<0.001$ — 4 weeks vs. 2, 1 weeks or 24 hours; $P = 0.031$ — 4 weeks vs. 3 weeks)

Abbreviations: see Figure 1 and Table 1

Table 3. Characteristics of newly diagnosed paroxysmal AF depending on monitoring time

Clinical characteristics	Diagnosed within 1 week (n = 44), % (95% CI)	Diagnosed between 1st–4th week (n = 42), % (95% CI)	*P*-value
Male sex	58.9 (44.1–72.3)	46.5 (33.7–59.9)	0.23
Female sex	41.1 (27.7–55.9)	53.5 (40.1–66.3)	
Age group, years			
65–74	44.4 (31–58.8)	36.4 (24.8–49.9)	0.70
75–84	36.5 (24.4–50.6)	39.4 (27.1–53.1)	
≥85	19 (9.7–34)	24.2 (13.9–38.8)	
Comorbidities			
Stroke	9.9 (4.9–18.7)	13.1 (7.4–22.2)	0.52
Coronary heart disease	15.4 (7.4–29.2)	8.2 (2.7–22.6)	0.33
Hypertension	87.0 (76.1–93.4)	84.7 (71.6–92.4)	0.72
Obesity	36.9 (25.1–50.5)	36.2 (24.6–49.6)	0.94
Diabetes	22.7 (13.7–35.2)	24.4 (15.6–36.2)	0.82
Chronic kidney disease	29.2 (19.1–42.1)	43.8 (30.3–58.4)	0.12
Heart failure	17.6 (7.8–35.1)	12.5 (7.1–21.3)	0.49
NT-proBNP >125 ng/ml	70.8 (55.5–82.5)	68.7 (54.4–80.2)	0.83
CHA_2DS_2-VASc, mean (SD)	3.7 (1.59)	3.9 (1.70)	0.70

Abbreviations: see Table 1

diagnosed AF in the United States in a population ≥65 years as 8.7% (95% CI, 8.6%–8.8%) and the prevalence of undiagnosed AF as 1.3% (95% CI, 0.9%–1.9%) [3]. The results from the ARIC study cohort, conducted in 2016–2017, show even higher numbers: total AF prevalence in individuals aged 75–94 years was estimated as 21.2% and 17.2% in white men and women, respectively [19].

The prevalence of AF estimated in our study (19.2%) is significantly higher than reported in the studies mentioned above, except for the ARIC study that also utilized continuous long-term ECG monitoring. There are several possible explanations for the higher prevalence in our data. First, it may reflect possible differences between the populations of the United States and Poland. This can be supported by ethnic differences (lower risk of AF in black people in the US while Polish citizens are almost all ethnically Caucasian) and differences in cardiovascular risk factors (higher prevalence of hypertension in Poland and a lower burden of obesity). However, previously reported estimates of AF prevalence in European countries, based on indirect estimators, also tended to be lower than in our study. For example, analysis of medical records from UK general practices resulted in an estimated prevalence of AF in subjects aged ≥85 years as 22.1% in men and 16.5% in women [20] while for a similar age group, our estimate was 31.9%.

The relatively high estimates in our study may also result from methodological differences. We undertook considerable efforts to minimize both selection and information biases. Selection bias was minimized by limiting exclusion criteria and interviewing patients at their homes, allowing even the most physically and mentally impaired subjects to be included in the sample. Information bias was reduced by a precise diagnosis of AF based on current clinical guidelines, a detailed review of medical documentation, and long-term ECG monitoring in every study participant, which could substantially decrease underreporting of AF. For example, 30-day monitoring increased the number of detected paroxysmal AF about 7-fold compared to standard 24-hour ECG recording. The diagnostic approach implemented in our study allowed us to detect 21% of the previously undetected AF that substantially contributed to the total number of cases.

Study strengths & limitations

To our knowledge, this is the first study estimating AF prevalence based on a nationally representative random sample, where all study participants were diagnosed in concordance with current clinical guidelines [21, 22].

All study visits and procedures were performed at patients' homes, allowing even severely disabled or demented patients to participate. This minimized selection bias of the study sample toward healthier subjects. Another unique feature is the evaluation of the relationship between the duration of ECG monitoring and the probability of detection of paroxysmal AF in the general population. Several earlier studies explored the importance of ECG monitoring longer than 24 hours, but they did it in highly selected populations such as patients with cryptogenic stroke or implantable devices [11, 23].

Our study also has several limitations. First, the response rate of 41% was relatively modest. This can potentially lead to selection bias. In recent years, it has become harder to reach high response rates in general population health surveys. For example, during NHANES 1999–2000, the reported unweighted response rate was 76% while in the recent edition (NHANES 2017–2018), this value was 48.8%, and even lower in older age groups [16].

Another limitation is the lack of complete, 30-day ECG monitoring in all patients. There is a possibility that some of the patients who were monitored for a shorter period without AF event, would have had AF detected if monitored for a longer time. This can result in some underestimation of AF prevalence.

Finally, our analysis is based on a representative sample of Polish citizens, and its results can be directly applied only to this population. The Polish population is entirely white, ethnically non-diverse, with universal access to healthcare. The prevalence of hypertension is relatively high (33% in adults 18+, using a 140/90 mm Hg threshold) while the prevalence of obesity (25%) is modest in European countries and much lower than in the United States.

CONCLUSIONS

The presented results suggest that AF prevalence can be higher in the population than previously estimated. Moreover, the longer-than-usual duration of ECG monitoring allows the detection of substantially more patients with previously unknown paroxysmal AF.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

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Incidence and course of acute coronary syndrome cases after the first wave of the COVID-19 pandemic

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Editorial
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ABSTRACT

Background: The collateral damage caused by the COVID-19 pandemic affected cardiovascular disease patients, mainly acute coronary syndrome (ACS) cases. Additionally, lockdown caused treatment-related concerns and reluctance to seek medical help, factors that can delay treatment.

Aim: We aimed to analyze the incidence and course of ACS after the first COVID-19 wave.

Methods: The report is based on a multi-institutional registry of 10 interventional cardiology departments. ACS patient data were gathered from June to October 2020, i.e. in the period following the first lockdown in Poland (March 30–May 31, 2020) and compared with the corresponding 2019 timeframe.

Results: Patients (2801 and 2620) hospitalized for ACS in 2019 and 2020 (June–October) represented 52.8% and 57.9% of coronary artery disease admissions, respectively. In 2020 vs. 2019, more cases of arterial hypertension (80.2% vs. 71.5%; P <0.001), diabetes (32.7% vs. 28.2%; P <0.001) hyperlipidemia (53.2% vs. 49.8%; P = 0.01), and smoking history (29.5% vs. 25.8%; P = 0.003) were detected. Median troponin and cholesterol values, as well as glycemia, were higher in 2020. Patients were more likely to undergo percutaneous treatment (91.2% vs. 87.5%; P <0.001) and were less often referred for surgery (3.7% vs. 4.9%; P = 0.03). No differences in deaths from repeat myocardial infarction, stroke, and/or composite endpoint (major adverse cardiac and cerebrovascular events [MACCE]) were noted. However, suffering from ACS in 2020 (June–October) was a risk factor for mortality based on multivariable analysis.

Conclusions: The COVID-19 pandemic affected ACS patient profile, course of treatment, and increased risk for mortality.

Key words: acute coronary syndrome, coronavirus, COVID-19, lockdown, myocardial infarction

INTRODUCTION

Acute coronary syndrome (ACS), particularly with ST-segment elevation, presents a major health risk for patients, and patients should be referred for immediate medical attention. According to the European Society of Cardiology (ESC) clinical guidelines, those patients should present to invasive cardiology departments as soon as possible [1, 2]. Any delay in treatment may be associated with adverse consequences, including mortality. However, during the COVID-19 pandemic, which was caused by SARS-CoV-2, a significant decrease in the number of ACS cases referred

WHAT'S NEW?

Reports referring to the COVID-19 pandemic rarely focus on its first stage. The period immediately following lockdown was characterized by limited healthcare access. We analyzed the time interval separating the two waves of the pandemic in Poland to determine the impact of the first lockdown on acute coronary syndrome (ACS) incidence and its treatments and outcomes. Our study showed that only the first wave of the pandemic significantly affected coronary artery disease patients. Higher numbers of both unstable angina and ST-segment elevation infarctions, when compared with the corresponding period of the previous year, were found. A higher frequency of non-communicable diseases was noted, indicating that inadequate treatment might have triggered ACS. These patients were more often treated percutaneously and less often referred for surgery. Furthermore, suffering from acute coronary syndrome right after the lockdown was a risk factor for mortality when compared with the corresponding timeframe of the previous year.

to health facilities and a significant delay in their treatment were reported worldwide [3–10]. This delay may have led to huge consequences in both hospital outcomes and out-patient mortalities. The Polish National Primary Statistical Department reported over 67 000 more deaths in 2020 than in 2019, which greatly exceeds mortality caused by the coronavirus infection [11]. Those numbers appeared greater when the following calendar years were compared. Furthermore, the lack of proper medical care and treatment for both stable angina and non-communicable diseases raised concerns regarding the incidence and severity of ACS cases following the lockdown. To address this issue we investigated the impact of only the first lockdown on the incidence of ACS, patient profiles, and clinical outcomes.

METHODS

The multi-institutional registry

All information gathered for the report was sourced from the database network, which connects 10 invasive cardiology departments in Poland. The database includes hospitalization parameters from patients admitted due to acute coronary syndrome (defined as ST-segment elevation myocardial infarction [STEMI], non-ST-segment elevation myocardial infarction [NSTEMI], and unstable angina) from June to October 2020 and the corresponding timeframe in 2019.

Analyzed parameters

Data were anonymous, and only the patient unique number was assigned by the computer system. We included in the analysis: date of admission and discharge, hospitalization department, discharge characteristics, data regarding diagnosis (primary diagnosis and diagnosis after the hospitalization), SARS-CoV-2 infection status, comorbidities, procedure characteristics, anamnesis, pharmacotherapy, laboratory tests, echocardiography, hospitalization course and complications (such as death, repeat infarction, bleeding, stroke, any type of vascular complications), discharge to an intensive care unit and the composite endpoint of major adverse cardiac and cerebrovascular events (MACCE) defined as death, and/or myocardial infarction (MI; repeat MI in patients presenting with MI on admission or MI in patients presenting with unstable angina on admission) and/or stroke.

Routine COVID-19 testing

In 2020, all the patients underwent routine PCR (polymerase chain reaction) tests upon their admission to the hospital. In emergent cases, antigen tests were also performed to avoid any delay in diagnosis and treatment. Further COVID-19 testing depended on the patient's symptoms or contact with infected patients or personnel.

Research ethics board approval

The approval of the research ethics board was not mandatory for the analysis as the report was fully retrospective and contained datasets with anonymized information. No additional intervention was administered to any of the study patients. Following the National Code on Clinical Research, research ethics board consent is not obligatory for real retrospective studies.

Statistical analysis

Categorical data are shown as numbers (percentages). Continuous data are presented as mean (standard deviation) or median (interquartile range [IQR]). The normal distribution of analyzed parameters was verified with the Saphiro-Wilk test. Normal distribution datasets were compared using Student's t-test while non-normally distributed data were compared using the Mann-Whitney U test. The χ^2 test was used to analyze categorical data.

To address the impact of continuous and binary predictors (including hospitalization timeframe) on outcomes, the Cox proportional-hazards regression model was used. Potential predictors of mortality and composite endpoint (MACCE) were searched. The observation was conducted during hospitalization; censoring was made in cases that did not reach the event. The variables included in the model were admission timeframe (June–October 2020 or June–October 2019), myocardial infarction at baseline, Canadian Cardiovascular Society (CCS) class IV for angina, glycemia at baseline, cholesterol value at baseline, troponin values on admission, baseline ejection fraction, male sex, and age.

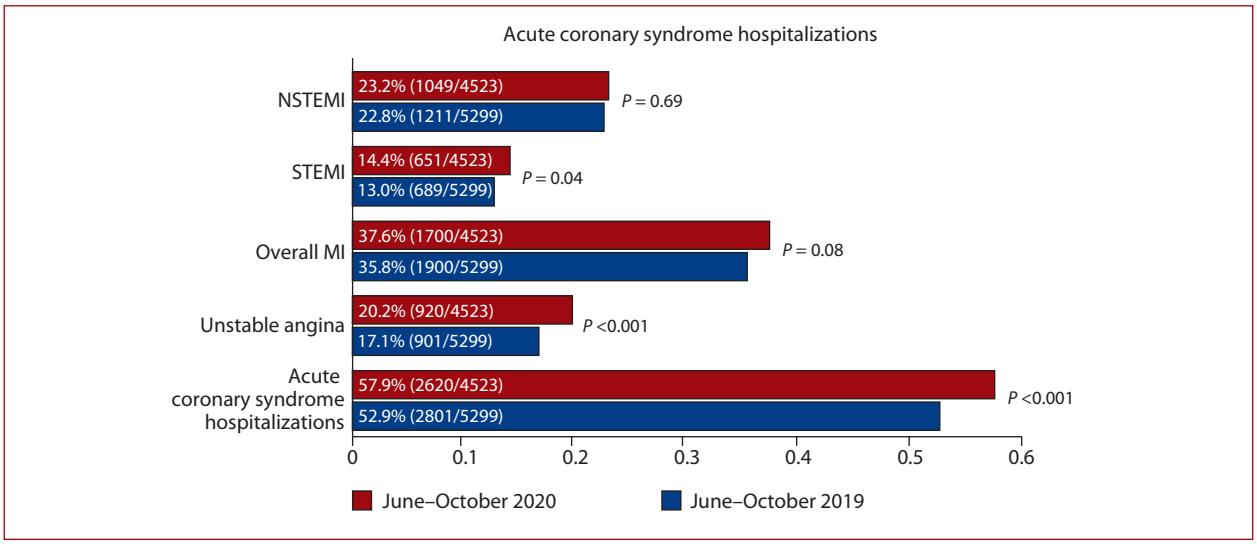

Figure 1. Hospitalizations for acute coronary syndrome with relation to the total number of hospitalizations for coronary artery disease. Data are presented as percentages (numbers)

Abbreviations: MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI; ST-segment elevation myocardial infarction

A stepwise variable selection procedure was used (variables were entered if P <0.3). MedCalc v.18.5 software (MedCalc Software, Ostend, Belgium) was used for data processing. A P-value of ≤0.05 was considered statistically significant.

Data presentation

The results from the current report are presented in three sections. The first includes data from patients' admission records and gives the baseline characteristics and their comparison in the evaluated time intervals. The second part compares the treatment characteristics in the same time intervals. Finally, the third section refers to hospitalization outcomes and potential complications as described on a timeline from admission date.

RESULTS

Overall, there were 5299 patients hospitalized in June–October 2019 (2801 acute coronary syndrome cases — 52.9%; 2498 elective cases — 47.1%) and 4523 patients hospitalized in June–October 2020 (2620 acute coronary syndrome cases — 57.9%; 1903 elective cases — 42.1%). These data reflect a significantly higher number of ACS hospitalizations related to overall hospitalizations for coronary artery disease following lockdown when compared with the corresponding time interval of the previous calendar year (Figure 1). The main reason for this observation was an increase in the incidence of unstable angina and STEMI with a similar number of NSTEMI cases (Figure 1).

The patients were similar in terms of age, sex, obesity, and symptoms when compared to June–October 2019. However, they presented more frequently with arterial hypertension, hyperlipidemia, diabetes, and were active smokers (Table 1). They had greater baseline values of high-sensitivity troponin T, cholesterol, and higher glycemia. The myocardial contractility, presented as ejection fraction, was similar in both timeframes. There were 15 (0.6% patients) SARS-CoV-2 infections in June–October 2020. Please note that none of the analyzed departments was a dedicated COVID-19 facility.

The pandemic affected not only the patient profile but also the course of treatment. The patients mostly underwent percutaneous revascularization. In this group, one-stage treatment of two arteries was more frequent than two-stage treatment during one hospitalization, which also contributed to relatively shorter hospitalization (Tables 2 and 3). A lower number of patients was referred for coronary artery bypass grafting procedures (Table 2). Patients who were not qualified for angioplasty or bypass grafting and received pharmacotherapy as dedicated treatment were included in the "non-invasive treatment group" (Table 2).

The maximal observation time was 24.0 days in 2019 and 27 days in 2020. Median observation time was 3.63 (1.6–4.9) days and 3.2 (1.5–4.6) days, respectively. The comparative analysis of hospitalization outcomes did not show significant differences in mortality, incidence of myocardial infarction or stroke, or the composite endpoint of MACCE. However, a trend toward greater mortality was visible (Table 3). More frequent hematomas of access sites were reported in 2019 (Table 3).

As mentioned, the hospitalization period was longer in the analyzed timeframe of 2019 when compared to 2020 (median [IQR], 3.63 [1.58–4.92] days vs. 3.16 [1.51–4.58] days; P <0.001).

In a multivariable analysis, suffering from ACS in 2020 was a risk factor for mortality (Figures 2, 3). Other significant risk factors for mortality included myocardial infarction at baseline and advanced age. Greater ejection fraction at baseline was a factor that decreased the risk

Table 1. Patient baseline characteristics

	2019 (June–October) 2801 patients	2020 (June–October) 2620 patients	*P*-value
Age, years, median (IQR)	67.0 (60.0–74.0)	67.0 (61.0–74.0)	0.85
Male sex, n (%)	1798 (64.2)	1637 (62.5)	0.19
Arterial hypertension, n (%)	2004 (71.5)	2102 (80.2)	<0.001
Hyperlipidemia, n (%)	1395 (49.8)	1393 (53.2)	0.01
Cholesterol at baseline, mg/dl, median (IQR)	167.0 (130.0–206.0)	183.0 (147.0–221.0)	<0.001
Low-density lipoprotein cholesterol, mg/dl, median (IQR)	107.2 (71.6–146.3)	111.5 (79.0–145.6)	0.13
High-density lipoprotein cholesterol, mg/dl, median (IQR)	42.0 (36.0–49.0)	43.0 (36.0–53.0)	0.19
Triglycerides, mg/dl, median (IQR)	115.0 (82.0–156.2)	114.0 (78.0–165.0)	0.99
Diabetes, n (%)	790 (28.2)	856 (32.7)	<0.001
Glycemia at baseline, mg/dl, median (IQR)	102.0 (87.0–123.5)	109.0 (100.0–143.5)	<0.001
Chronic kidney disease, n (%)	312 (11.1)	326 (12.4)	0.14
Creatinine, mg/dl, median (IQR)	0.9 (0.7–1.1)	0.9 (0.8–1.1)	0.004
COPD/asthma, n (%)	199 (7.1)	188 (7.2)	0.92
Malignancy, n (%)	44 (1.6)	28 (1.1)	0.11
Obesity, n (%)	864 (30.8)	858 (32.7)	0.13
Weight, kg, median (IQR)	80.0 (70.0–90.0)	81.0 (72.0–93.0)	0.01
BMI, kg/m^2, median (IQR)	28.0 (25.0–31.0)	28.0 (25.0–32.0)	0.10
Active smoking, n (%)	724 (25.8)	773 (29.5)	0.003
CCS class for angina, n (%)			
CCS II	120 (4.4)	89 (3.4)	0.21
CCS III	1651 (58.9)	1543 (58.9)	
CCS IV	1030 (36.7)	988 (37.7)	
Baseline echocardiography			
LVEF %, median (IQR)	50.0 (43.0–55.0)	50.0 (42.0–55.0)	0.71
LV-end systolic diameter, mm, median (IQR)	35.0 (30.0–40.0)	35.0 (30.0–40.0)	0.67
LV-end diastolic diameter, mm, median (IQR)	51.0 (47.0–55.0)	51.0 (47.0–55.0)	0.85
Left atrium, mm, median (IQR)	40.0 (36.0–43.0)	40.0 (36.0–44.0)	0.91
Right ventricle, mm, median (IQR)	29.0 (26.0–32.0)	29.0 (26.0–32.0)	0.26
Intraventricular septum, mm, median (IQR)	11.0 (10.0–12.0)	11.0 (10.0–12.0)	0.62
Posterior wall, mm, median (IQR)	11.0 (10.0–12.0)	11.0 (10.0–12.0)	0.47
Mitral valve regurgitation, n (%)	213 (7.6)	193 (7.4)	0.74
Aortic valve regurgitation, n (%)	26 (0.9)	26 (1.0)	0.81
Aortic valve stenosis, n (%)	81 (2.9)	76 (2.9)	0.98
Symptomatic HF, n (%)	1034 (36.9)	971 (37.1)	0.91
NYHA II class, n (%)	651 (62.9)	614 (63.2)	
NYHA III class, n (%)	300 (29.0)	244 (25.1)	0.009
NYHA IV class, n (%)	83 (8.1)	113 (11.7)	
HFrEF, n (%)	549 (53.1)	495 (50.9)	
HFmrEF, n (%)	409 (39.6)	445 (45.9)	<0.001
HFpEF, n (%)	76 (7.3)	31 (3.2)	
Blood cell count parameters, median (IQR)			
Hemoglobin, g/dl	13.1 (11.8–14.3)	13.3 (11.9–14.5)	0.12
Red blood cell count, ×10^{12}/l	4.32 (3.9–4.7)	4.22 (3.8–4.6)	<0.001
White blood cell count, ×10^9/l	7.5 (5.3–9.6)	7.4 (5.1–9.8)	0.20
Platelet count, ×10^9/l	205.0 (166.0–245.0)	206.0 (170.0–250.0)	0.31
Hs-troponin T at baseline, pg/ml, median (IQR)	206.5 (14.0–2790.0)	725.0 (79.5–6505.0)	<0.001

Data are presented as median (interquartile range) and number (percentage)

Abbreviations: BMI, body mass index; CCS, Canadian Cardiovascular Society class for angina; COPD, chronic obstructive pulmonary disease; HF, heart failure; HFmrEF, heart failure with mid-range ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; Hs-troponin T, high sensitivity troponin T; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association class for heart failure

for mortality (Figure 2). The stepwise analysis method removed cholesterol and troponin concentrations from the model (data were entered if P <0.3).

Risk factors for MACCE included myocardial infarction at baseline and advanced age. However, a trend for significance of ACS timeframe as a risk factor was apparent (Figures 4, 5). The stepwise analysis method removed CCS class IV for angina, baseline troponin and cholesterol concentrations, glycemia, ejection fraction, and male sex from the model (data were entered if P <0.3).

DISCUSSION

The first report describing the impact of the pandemic on ACS cases in Poland was already published by Hawranek et al. [12]. The authors presented valuable data showing that the patients in 2020 were younger than in previous years, more often transferred from another hospital, were rarely referred for coronary artery bypass graft (CABG) and waited for longer periods from admission to coronarography. They also demonstrated a trend toward a higher incidence of STEMI, but no statistical significance was ob-

Table 2. Acute coronary syndrome treatment in time intervals

	2019 (June–October) 2801 patients	2020 (June–October) 2620 patients	*P*-value
Non-invasive treatment (angiography, pharmacotherapy)	214 (7.6)	134 (5.1)	<0.001
Percutaneous revascularization	2450 (87.5)	2390 (91.2)	<0.001
Infarct-related artery distribution (STEMI cases)			
LAD	272 (39.5)[a]	283 (43.5)[a]	0.33
Cx	190 (27.6)[a]	166 (25.5)[a]	
RCA	227 (32.9)[a]	202 (31.0)[a]	
Number of arteries treated (initial procedure)			
Single artery	2184 (89.1)[b]	1969 (82.4)[b]	<0.001
Two arteries	227 (9.3)[b]	389 (16.3)[b]	
Three arteries	39 (1.6)[b]	32 (1.3)[b]	
Two stages of treatment during hospitalization	534 (19.1)	263 (10.0)	<0.001
Intraprocedural glycoprotein IIb/IIIa inhibitor (intravenous)	483 (17.2)	413 (15.8)	0.14
Referred for CABG	137 (4.9)	96 (3.7)	0.03
Detailed pharmacotheraphy			
Statins	2537 (90.6)	2358 (90.0)	0.47
atorvastatin	1341 (52.8)	1228 (52.1)	0.76
rosuvastatin	1154 (45.5)	1086 (46.1)	
simvastatin	42 (1.7)	44 (1.8)	
Acetylsalicylic acid	2496 (89.1)	2361 (90.1)	0.23
P2Y12 receptor inhibitors	2564 (91.5)	2365 (90.3)	0.10
clopidogrel	1121 (43.7)	997 (42.2)	0.26
prasugrel	773 (30.1)	764 (32.3)	
ticagrelor	670 (26.2)	604 (25.5)	
Anticoagulation therapy:	340 (12.1)	354 (13.5)	0.13
VKA	31 (9.1)	31 (8.7)	0.87
NOAC	309 (90.9)	323 (91.3)	
Complete revascularization at discharge	2158 (77)	1970 (75.2)	0.11

Data are presented as numbers (percentage)
[a]Percentage of STEMI cases. [b]Percentage of patients treated invasively

Abbreviations: CABG, coronary artery bypass grafting; Cx, circumflex artery; LAD, left anterior descending artery; NOAC, non-vitamin K antagonist oral anticoagulants; RCA, right coronary artery; STEMI, ST-segment elevation myocardial infarction; VKA, vitamin K antagonists

Table 3. Hospitalization outcomes

	2019 (June–October) 2801 patients	2020 (June–October) 2620 patients	*P*-value
Mortality, n (%)	50 (1.9)	70 (2.7)	0.08
Myocardial infarction, n (%)	26 (0.9)	28 (1.1)	0.60
Stroke, n (%)	7 (0.2)	3 (0.1)	0.25
MACCE, n (%)	87 (3.1)	101 (3.8)	0.13
Minor bleeding, n (%)	11 (0.3)	5 (0.2)	0.17
Major bleeding, n (%)	2 (0.07)	3 (0.1)	0.60
Vascular complications — false aneurysm, n (%)	6 (0.2)	10 (0.4)	0.26
Stent thrombosis, n (%)	9 (0.3)	8 (0.3)	0.92
Hematoma — access site, n (%)	36 (1.3)	14 (0.5)	0.004
Duration of hospitalization, median (IQR)	3.63 (1.6– 4.9)	3.2 (1.5– 4.6)	<0.001

Abbreviations: MACCE, major adverse cardiac and cerebrovascular events (mortality, myocardial infarction, stroke)

served. The results from our study are similar with respect to corresponding endpoints; we observed a lower number of CABG cases and a higher number of STEMI cases, both of which reached statistical significance in our report. We did not observe differences in patient ages between studies. However, some differences in study design were noted, which may be the reason for the differences. One difference included the analyzed timeframe, as our study included patients from June to October, which is the interval separating the two major surges in the pandemic and mainly reflects the population's health situation following the first lockdown. In this case, healthcare availability was improved when compared to the lockdown itself, which may have contributed to different observations regarding both patient admission and effects of treatment.

Another report described hospitalizations and interventional procedures in Poland in the region inhabited by 2.5 million people during the SARS-CoV-2 pandemic. The authors noticed a lack of significant decrease in the number of STEMI patients, significant reduction of interventional revascularization procedures in NSTEMI patients, and significant decrease in the total number of hospitalizations unrelated to coronary interventions [13].

The Cox proportional-hazards regression model was designed to evaluate the strong indicators of adverse outcomes. The impact of the timeframe for admission on

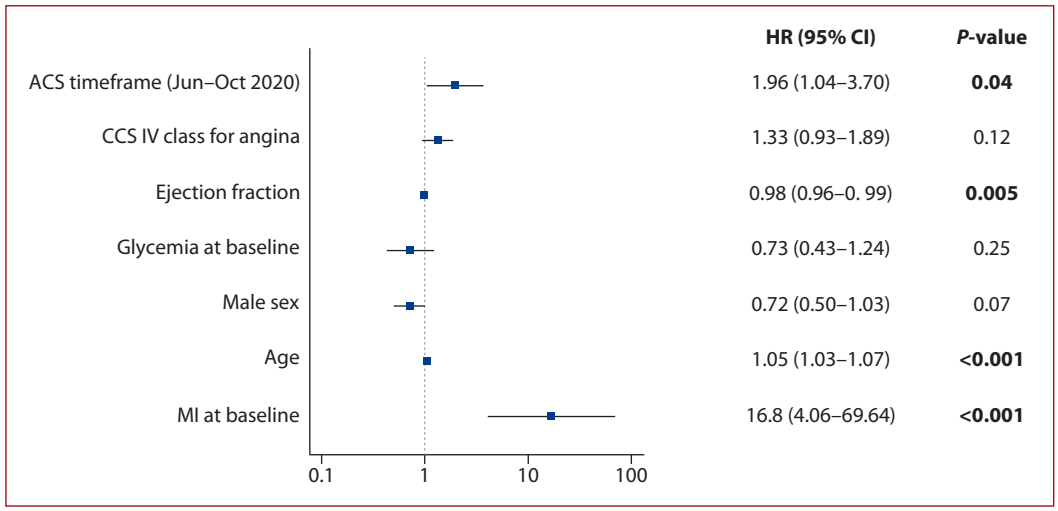

Figure 2. Forest plot of hazard ratios for mortality (Cox proportional hazards regression model). Markers represent point estimates of hazard ratios. Horizontal bars indicate 95% confidence intervals

Abbreviations: ACS, acute coronary syndrome; MI, myocardial infarction; other — see Table 2

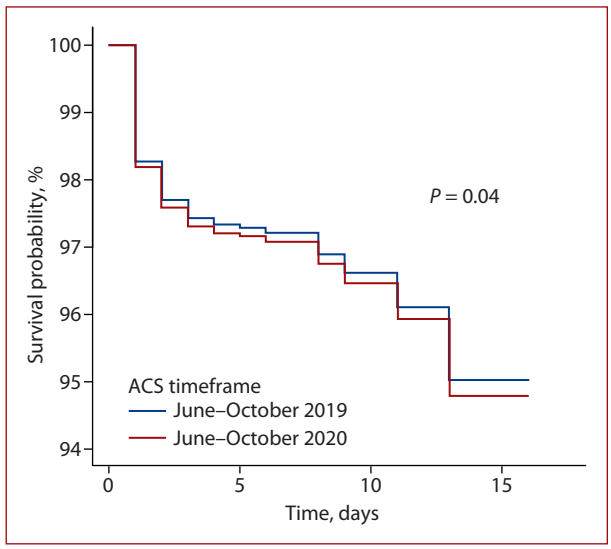

Figure 3. Cox proportional hazards cumulative survival curves with respect to different acute coronary syndrome timeframes adjusted for myocardial infarction at baseline, CCS class IV for angina, glycemia at baseline, baseline ejection fraction, male sex, and age

Abbreviations: CCS, Canadian Cardiovascular Society Class for angina; other — see Figure 2

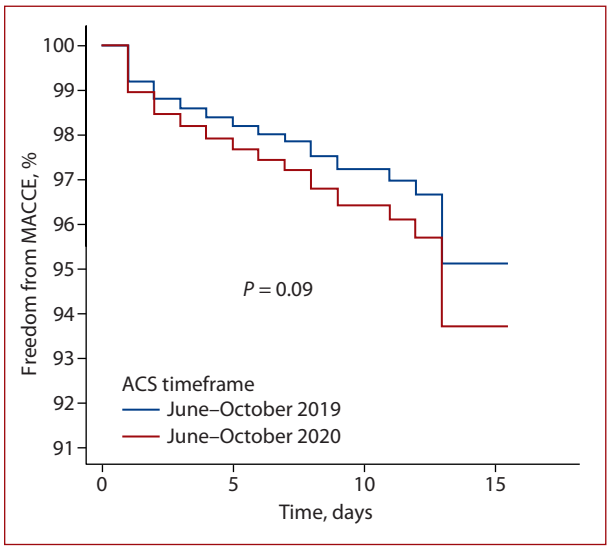

Figure 5. Cox proportional hazards freedom from MACCE curves with respect to different acute coronary syndrome timeframes adjusted for myocardial infarction at baseline and age

Abbreviations: see Figures 2, 4

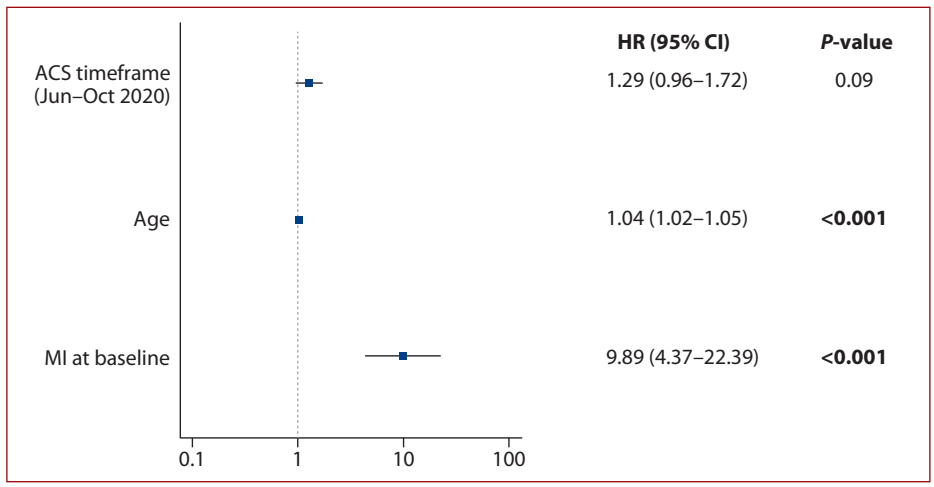

Figure 4. Forest plot of hazard ratios for MACCE (Cox proportional hazards regression model). Markers represent point estimates of hazard ratios. Horizontal bars indicate 95% confidence intervals

Abbreviations: MACCE, major adverse cardiac and cerebrovascular events (death, repeat infarction, stroke); other — see Figure 2

adverse outcomes may be associated with limited access to healthcare and fear of COVID-19 as the reasons why patients did not present for medical care when experiencing various symptoms. Another reason could be a possible delay in directing patients to an invasive cardiology department.

Regarding the analyzed time interval, two of referenced studies reported very similar observations. There was a decrease in admissions for myocardial infarction during the first wave of the pandemic, but a significant reversal in this decline in April and May 2020, following the national lockdown [7, 8].

Importantly, the number of both post-lockdown and overall pandemic deaths caused by ACS may be heavily underestimated. Some reports pointed out an increase in the number of out-of-hospital deaths and cardiac arrests when compared to the period before the pandemic [14].

The same study reported that in-hospital survival after out-of-hospital cardiac arrest was 64% lower than before the pandemic [14]. Other reports show an increase in hospital deaths following the lockdown, which ranged from 4.1% to 9.6% when compared with the corresponding time interval before the pandemic [7, 15–17]. This finding may be caused by both limited access to healthcare facilities and also by delay in patients' reaction to symptoms. This important aspect showing the fear of COVID-19 as a reason for patients not presenting for medical care when experiencing various symptoms, including chest pain, has already been reported by multiple studies [18–21].

The issue of the number of non-communicable diseases in the analyzed time intervals should not be avoided. The global population was forced to modify social behavior for both epidemiological and economic reasons. In most cases, modifications were associated with changes in diet and avoidance of physical exercise.

It is not feasible that the lockdown alone could have resulted in such a rapid development of the disease itself. However, the lack of proper treatment for non-communicable diseases surely produced an impact on the incidence of ACS cases by triggering adverse events. Both systolic and diastolic hypertension independently predicted adverse outcomes, including myocardial infarction [22]. A linear increase in the risk of MI with an increase in blood pressure has been reported [23]. Poor glycemic control in diabetic patients increases inflammatory responses, induces apoptosis, causes endothelial dysfunction, and stimulates platelet aggregation and accumulation [24–28], and as such, may significantly contribute to worsening the frequency and prognosis in ACS patients. Notably, several patients in both groups were not in CCS class IV for angina, which may be related to both a great incidence of CCS III unstable angina and high incidence of uncontrolled diabetes, which affects the symptoms significantly [29, 30]. Smoking is obviously one of major risk factors for coronary artery disease, and the risk of acute myocardial infarction increases with the number of cigarettes smoked per day [31–33]. Notably, it has been proven that during the pandemic people smoked more, driven by COVID-19-related stress, more time spent at home, and boredom [34]. These stressful situations probably became aggravated when the lockdown ended and new challenges in daily routine, still affected by the pandemic, emerged.

The association between populational health and mental and social issues only worsened the situation [35–40]. From this perspective, further increases, not only in incidence of acute coronary syndromes but also in occurrence of more complex cases can be expected.

In-hospital treatment for ACS also differed when compared to the corresponding timeframe of the previous calendar year. First, a higher number of patients qualified for percutaneous revascularization. This finding is expected as a higher incidence of STEMI could be one of the reasons for performing salvage percutaneous coronary intervention (PCI) instead of qualifying patients for surgical treatment by a heart team [1, 2]. However, some other negative effects of the pandemic can be observed. From patients' perspectives, multiple hospitalizations for diagnosis, further preparation for surgery, transfer from one hospital to another, long therapeutic processes, and rehabilitation are particularly dangerous in epidemiological terms. As such, most heart teams probably favored shorter therapeutic processes and qualified borderline cases for percutaneous treatment. Second, it was obvious that patients with lower peri-operative immunity are especially prone to infection, which may have significantly changed the mortality and morbidity rates. From a surgical perspective, surgical procedures during the pandemic should focus on the most urgent cases that cannot be postponed and cannot be treated percutaneously. This observation is supported by international reports, which also present a decrease in the number of surgically treated patients [41].

Study limitations

The design of the study (retrospective dataset analysis) has the limitations of such reports. Moreover, it was difficult to assess true long-term survival and complication incidence in those patients, as they were admitted to the hospital with a much higher occurrence of comorbidities when compared to the pre-pandemic period. This aspect may affect the incidence of repeat ACS cases, morbidity, and mortality in upcoming years.

In conclusion, it should be emphasized that the COVID-19 pandemic affects the ACS patient profile, course of treatment, and increases the risk for mortality. This effect already became apparent after the first wave of the pandemic in Poland. Further progression of this effect can be expected.

Article information

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Assessment of fetal left atrial volume and function using a novel left atrial volume tracking method

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ABSTRACT

Background: Several fetal cardiovascular structural defects may alter the hemodynamics of the cardiac chambers resulting in changes in chamber sizes. Quantitative measurements of the sizes of cardiac chambers can augment the diagnostic power of fetal echocardiography.

Aims: Using a new left atrial volume tracking (LAVT) method, time-left atrial volume curves (TLAVCs) can be automatically obtained. The goal of this study was to examine whether this method can be used to evaluate left atrial volume (LAV) and provide reference values for LAV and indices of left atrial function in normal human fetuses.

Methods: Two hundred and four normal human fetuses were enrolled. Using LAVT, the maximal left atrial volume (LAVmax) and minimal left atrial volume (LAVmin) were measured from TLAVCs. Left atrial ejection fraction (EF) was calculated. The maximal left atrial area (LAAmax) and minimal left atrial area (LAAmin) were measured using manual method tracing.

Results: Between 21 and 40 weeks, mean LAVmax increased from 0.27 ml to 4.15 ml, and mean LAVmin increased from 0.13 ml to 2.26 ml, respectively, while the EF remained stable at around 0.43. From 21 to 40 weeks, mean LAAmax increased from 0.61 cm^2 to 2.64 cm^2, and mean LAAmin increased from 0.34 cm^2 to 1.53 cm^2.

Conclusions: This study establishes reference values for fetal LAV during the second half of gestation. The LAVT method appears to be feasible in estimating fetal LAV and shows potential for assessing left atrial function.

Key words: fetal echocardiography, left atrial tracking, left atrial volume

INTRODUCTION

Fetal echocardiography has become a reliable technique for assessing structural defects and arrhythmias in the second and third trimesters of gestation [1–2]. Several fetal cardiovascular structural defects and arrhythmias may alter the hemodynamics of the atrial and/or ventricular chambers resulting in changes in chamber sizes [3–6]. The size and shape of the chambers in fetuses are related to perinatal death [7]. Quantitative measurements of the sizes of cardiac chambers may enable the physician to understand the growth pattern of normal fetal hearts and augment the diagnostic power of fetal echocardiography. Traditional methods include measurements of the diameters of cardiac chambers by M-mode and 2-dimensional echocardiography (2DE) methods [8–9]. Chamber volume calculation from 2DE does not rely on measuring a single dimension, but rather covers the entire cross-sectional area of the chamber; therefore, measurements using 2DE may better estimate volume changes. The accuracy of ventricular volume determination by 2DE using a biplane Simpson's rule algorithm was first shown in fetal sheep [10], and then this method was further developed in normal human fetuses [11]. In adults, the 2DE biplane Simpson's method was recommended by the American Society of Echocardiography to evaluate left atrial volume (LAV), and the accuracy has been validated by in-vitro models and angiography [12–14]. The left atrial volume tracking (LAVT) method is a newly developed method that is an automated measurement. It is evaluated

WHAT'S NEW?

In adults, 2-dimensional echocardiography (2DE) biplane Simpson's method was recommended by the American Society of Echocardiography to evaluate left atrial volume (LAV) and the accuracy has been validated by in-vitro models and angiography. This study applies a new left atrial volume tracking (LAVT) method, which is based on Simpson's rule algorithm, to establish normal values for human LAV during the second half of gestation. The LAVT method appears to be a feasible method to estimate fetal LAV and left atrial ejection fraction (EF) during the second half of gestation, suggesting its potential value in assessing left ventricular diastolic function of fetal hearts, especially under pathological conditions in the mother or fetus.

in images based on offline analysis and might be useful for measuring LAV curves precisely in adults [15]. Recently, it has also been used in fetal hearts [16–17]. In our study, we apply this method, which is based on Simpson's rule algorithm, to establish normal values for human LAV during the second half of gestation.

METHODS

Study population

The study population consisted of singleton pregnancies from 21 to 40 weeks of gestation undergoing fetal echocardiography scans at the Sir Run Run Shaw Hospital, Zhejiang University College of Medicine in Hangzhou, China. This study was approved by the Ethics Committee of the Sir Run Run Shaw Hospital and informed consent was obtained from all participants. Inclusion criteria were accurate gestational age (GA) based upon measurement of the fetal biparietal diameter (BPD) and femoral length; normal fetal growth, and absence of medical complications, such as diabetes mellitus, or hypertension. The exclusion criteria were fetal cardiac and extracardiac abnormalities; abnormal intrauterine fetal growth; inability to obtain a standard view due to variable fetal position.

A total of 204 fetuses that had normal cardiac morphology and normal sinus rhythm in the second and third trimesters were used as the research objects. Inspection of the atrial symmetry would be first made in a standard four-chamber heart view. If there was any asymmetry in atrial size, we would measure the width and length of the left and right atrium and then calculate the width ratio of the left and right atrium (RA/LA width ratio); if the RA/LA width ratio was in the range of 0.8~1.2, the fetus was regarded as having normal atrial morphology.

The principles of the left atrial volume tracking method

The LAVT method uses the adaptive density gradient (ADG) method with the ability of automatic construction of the LAV profile by applying a 2-dimensional tissue tracking technique. In the ADG method [18], only the pixels on the sector beam which has the necessary information for the tracking process would be tracked, resulting in reducing the number of pixels for tracking and saving tracking time (Supplementary material, *Video S1*). Therefore, the ADG method can produce faster calculation speed, higher accuracy, and higher frame rates compared to the conventional block-matching method [18]. An image clip of the apical four-chamber view in one cardiac cycle was stored in the commercially available EUB-900 ultrasound scanner (Hitachi Medical Corporation, Chiba, Japan). The automatic construction of the left atrial curve was performed offline using a prototype viewer (Hitachi Medical Corporation, Chiba, Japan). The left atrial endocardium was manually traced at first, and subsequent LAV at each frame was automatically calculated by the single-plane Simpson's rule, resulting in the construction of the LAV curve within one minute. The biplane Simpson's rule can also be applied in this procedure.

Echocardiography

Echocardiographic examinations were performed on the subjects with a Philips iE33 xMATRIX ultrasound system (Philips Medical System, Bothell, WA, USA) with a 1.0–5.0 or 3.0–8.0 MHz transducer. General schematic sonographic examination was performed to rule out fetal abnormalities and was followed by detailed fetal 2-dimensional and color Doppler echocardiography to exclude fetal heart anomalies [19]. The maximal left atrial area (LAAmax) and minimal left atrial area (LAAmin) were traced from the four-chamber view. We magnified the images to minimize calibration-induced measurement errors. Then, we used the commercially available EUB-900 ultrasound scanner (Hitachi Medical Corporation, Chiba, Japan) to obtain time-left atrial volume curves (TLAVCs). The fetal left atrium was imaged in orthogonal planes corresponding to those obtained postnatally for volume calculation equivalent to apical four- and two-chamber views. Imaging of the left atrium was considered satisfactory if all 4 chambers, the left ventricular apex, both atrioventricular valves, and confluence of pulmonary veins were seen in the four-chamber view. The display of the mitral valve, apex, and aortic valve served as coordinates in the two-chamber view. After optimizing the gain, dynamic range, and sensitivity time control, images were digitally recorded for 2 seconds (about 5 to 6 cardiac cycles) and stored on hard discs for later analysis. Then, the left atrial endocardium of the apical four-chamber and two-chamber view was manually traced at the first frame. This measurement was based on the innermost bright edge convention, which disregarded the orifices of the pulmonary veins but not the floating foramen ovale flap. Subsequently, LAV at each frame was

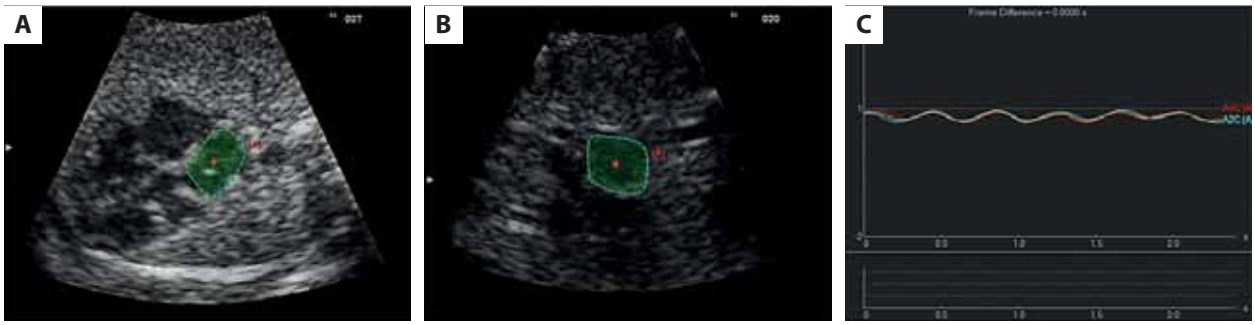

Figure 1. The manual trace of the left atrial endocardium at the level of four-chamber (**A**) and 2-chamber view (**B**) at the first frame of the dynamic images. Time-left atrial volume curves (**C**) were automatically obtained with the left atrial tracking method, which contained the volume corresponding to each frame, including the volume in 4-chamber view (the red curve), 2-chamber view (the blue curve) and the overall volume (the yellow curve) by the biplane Simpson's rule.

automatically calculated by the single-plane and biplane Simpson's rule. Finally, TLAVCs were automatically obtained (Figure 1). The LAVmax and LAVmin were measured from the volume waveform by the biplane Simpson's rule. Calculations were made in 3 to 6 consecutive cardiac cycles and averaged. Left atrial EF was calculated as the difference between LAVmax and LAVmin, divided by end-diastolic volume. In 20 randomly selected fetuses, both LAVmax and LAVmin were measured by the same observer (B.W.Z) twice and then by another observer (SPZ) to compare the measurements and to calculate interobserver and intraobserver agreement.

Statistical analysis

For each variable, a simple scatter plot graph was first obtained to observe roughly their correlations and tendencies with GA. Regression analysis was used to examine the correlation between measured volumes and GA and measured volumes and BPD. Separate linear, quadratic, cubic, and logarithmic regression models were fitted to identify the optimal one. Based on the equations acquired for both the mean and SD, population reference intervals for gestational age were estimated. Bland-Altman analysis was used to compare the measurement agreement and bias for a single observer and two observers [20–21]. P <0.05 was considered statistically significant. The data were analyzed using Excel for Windows 2003 (Microsoft Corp., Redmond, WA, USA) and IBM SPSS package 22.0 (SPSS, Inc., Chicago, IL, US).

RESULTS

Of all 204 fetuses, 17 fetuses were excluded because of inadequate imaging. Optimal TLAVCs were acquired in the other 187 fetuses (success rate was 92%). Limiting factors for TLAVCs acquisition included low image resolution at young GA, abundant fetal movement, numerous acoustic shadows, and a persistent unfavorable fetal position. It was found that all the target volumes correlated strongly both with GA and BPD. The best-fitted regression equations of the mean of the studied parameters against GA and BPD are shown in Supplementary material, *Table S1*. The curves of best fit for mean LAVmax and LAVmin against both GA (Figure 2) and BPD (Figure 3) as the independent variable were the quadratic curve. Meanwhile, the best model for mean LAAmax and LAAmin based on GA was linear regression. Based on the acquired equations the predicted mean LAVmax ranged from 0.27 ml at 21 weeks to 4.15 ml at 40 weeks, and the mean LAVmin ranged from 0.13 ml at 21 weeks to 2.26 ml at 40 weeks. Figure 4 demonstrated an increase in LAAmax and LAAmin with advancing GA. The detailed values are shown in Supplementary material, *Table S2*. Meanwhile, Pearson correlation analysis showed there was no significant correlation between mean left atrial EF and GA, and it remained fairly stable at around 0.43 with advancing GA (Figure 2). Bland-Altman analysis showed that there was a good agreement of the LAV data between two observers and for a single observer. The intra-observer variation coefficient for measured mean LAVmax and LAVmin was 5.0% and 6.6%, respectively; and the interobserver variation coefficient for measured mean LAVmax and LAVmin was 7.6% and 7.9%, respectively (Figure 5).

DISCUSSION

In the present study, we examined whether the newly developed LAVT method can be used to evaluate LAV and provide normal LAV reference indices for evaluation of left atrial function in normal human fetuses. Left atrial function can best be characterized by pressure-volume loops, similar to methods used to estimate left ventricular function [22–23]. However, invasive methods for determination of instantaneous left atrial pressures are required for this evaluation. In adults, computed tomography (CT) and magnetic resonance imaging (MRI) are considered more accurate than echocardiographic methods in the quantification of LAV [12, 24]. But for fetuses, those cardiac scanning modalities are infeasible because of their inability to conduct ECG gating technology or harmful radiation effects. Thus, with the introduction of various new technologies, echocardiography has been ever widely used in screening for fetal heart diseases [2]. Several initial studies indicated the applicability of the LAVT method in assessing LAV and its usefulness has been validated in adult investi-

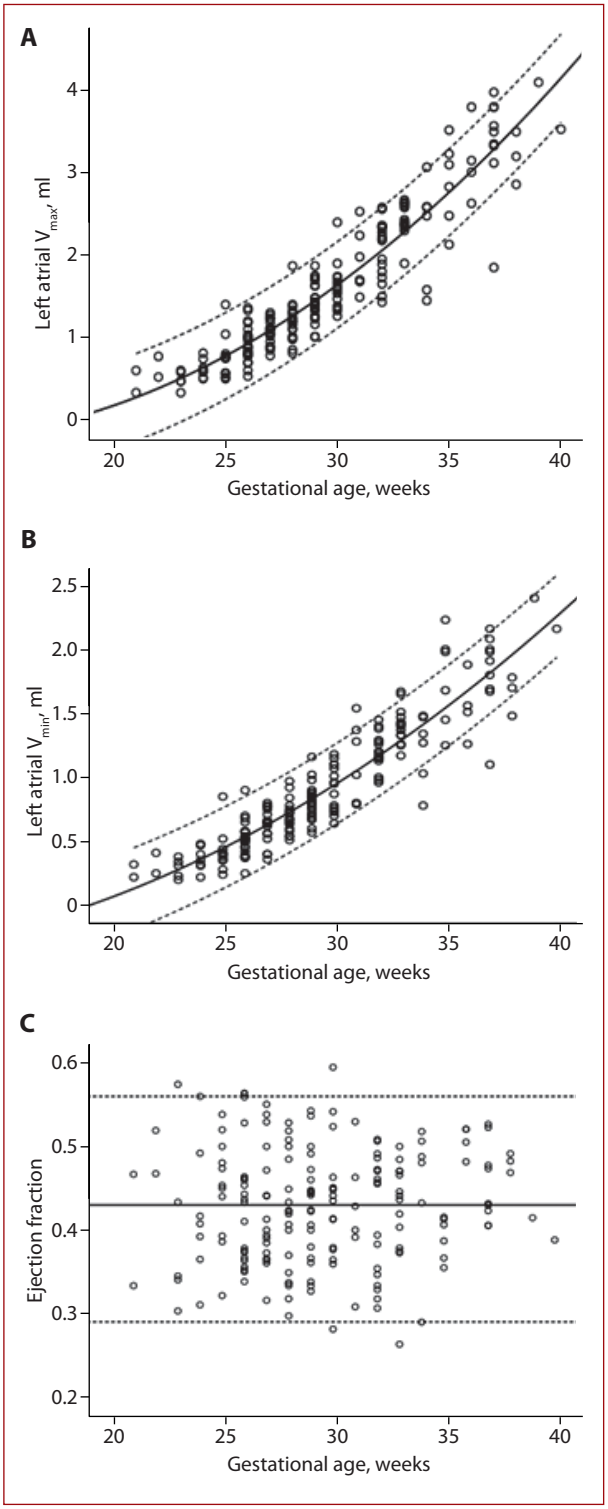

Figure 2. Volume measurements of the left atrium and ejection fraction plotted against gestational age. Atrial volume showed a consistently stronger correlation than that found with biparietal diameter (BPD). Solid lines represent the mean; dashed lines represent 5% and 95% confidence intervals (CI). **A.** Left atrial maximal volume. **B.** Left atrial minimal volume. **C.** Left atrial ejection fraction

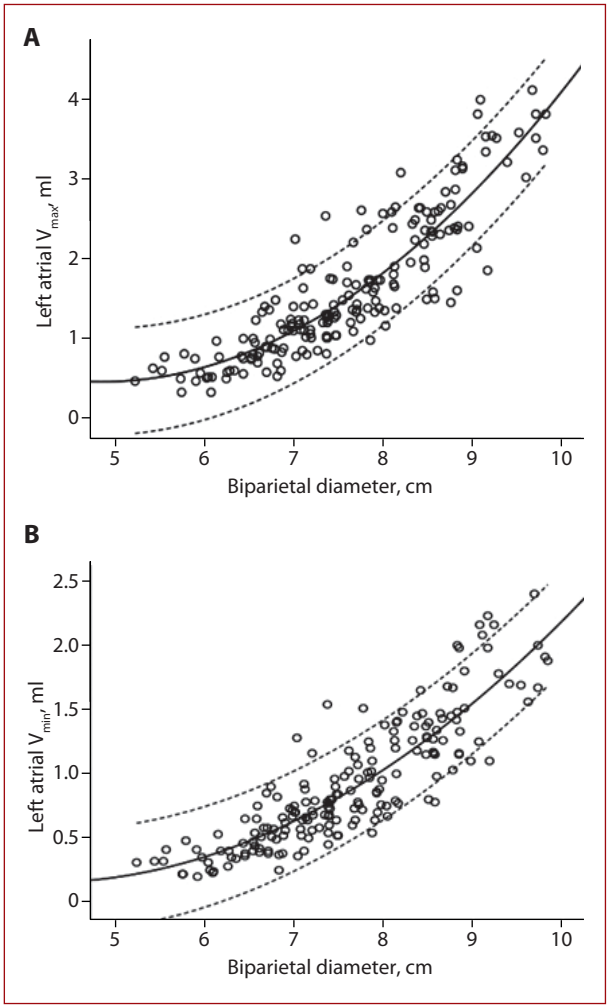

Figure 3. Volume measurements of the left atrium plotted against biparietal diameter (BPD). Solid lines represent the mean; dashed lines represent 5% and 95% confidence intervals. **A.** Left atrial maximal volume. **B.** Left atrial minimal volume

gation [15, 25–26]. To the best of our knowledge, this is the first investigation attempting to quantify LAV in a relatively large group of normal fetuses.

There was up to a 20-fold increase in fetal maximal and minimal LAV between 21 weeks and 40 weeks, which was faster during the last quarter of pregnancy. The quadratic shape of these growth curves resembles general fetal growth curves that are related to GA. However, they are different from the linear growth curves that have been reported previously for M-mode diameter measurements of the left atrial size calculated from 1 dimension [27]. The manually traced left atrial areas were found to correlate with GA. LAV increased with GA, which is consistent with our study [28–29]. It may add useful information to future

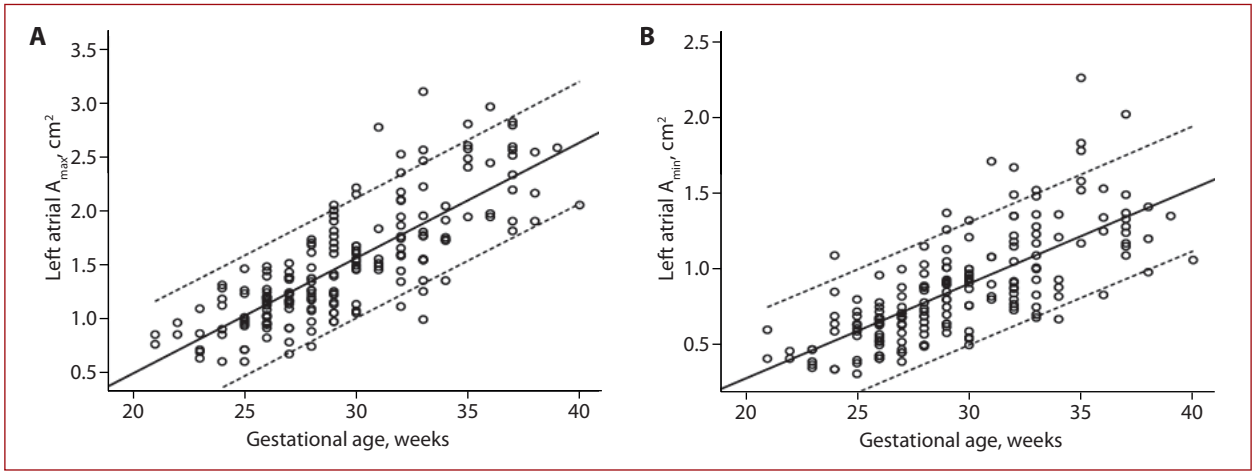

Figure 4. Area measurements of left atrium plotted against gestational age. Solid lines represent the mean; dashed lines represent 5% and 95% confidence intervals. **A.** Left atrial maximal area. **B.** Left atrial minimal area

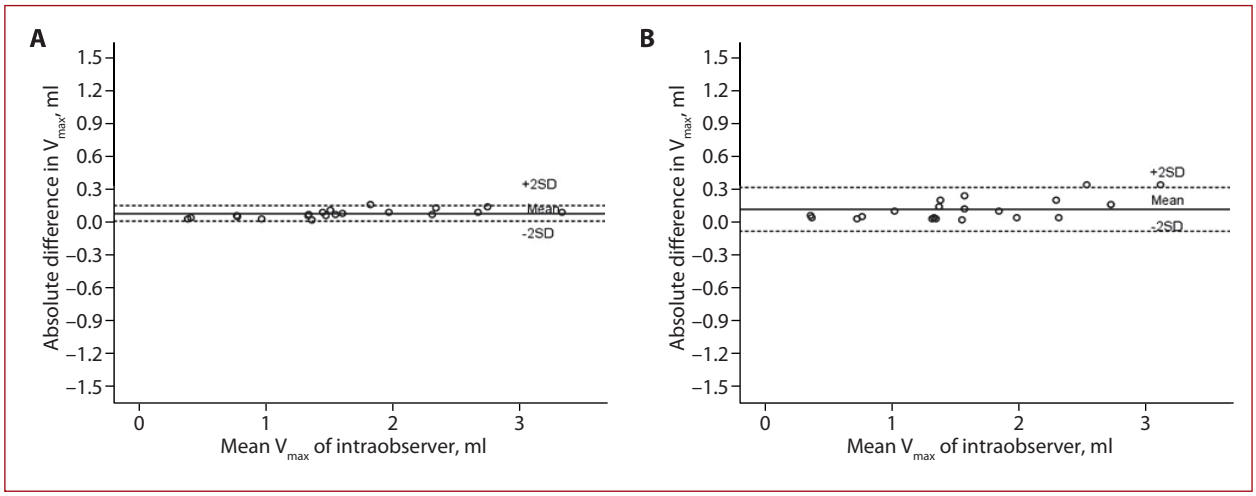

Figure 5. Bland-Altman plots of the absolute difference and 95% limits of agreement between paired measurements of left atrial Vmax by the same sonographer (**A**) and two sonographers (**B**)

studies of fetal LA [28–30]. Theoretically, left atrial mechanical function consists of three phases within the cardiac cycle [31]. First, during ventricular systole and isovolumic relaxation, the left atrium functions as a "reservoir" that receives blood from pulmonary venous return and stores energy in the form of pressure. Second, during the early phase of ventricular diastole, the left atrium operates as a "conduit" for transferring blood into the left ventricle (LV) after mitral valve opening via a pressure gradient. Third, during the late phase of ventricular diastole, LA performs as a "booster pump" through the contractile function which normally serves to augment the LV stroke volume by approximately 20% [31]. In normal adults, the TLAVCs consist of 2 peaks and 2 valleys, and phased LAV can be easily distinguished [26]. However, in fetuses that would be difficult without the guidance of the electrocardiogram since E and A waves of the diastolic mitral flow spectrum may fuse as a result of fast fetal heartbeat; thus the second valley becomes blurred in the curve (Figure 1).

In this study, as a fetal electrocardiogram cannot routinely be available, phasic left atrial functions cannot be acquired from the TLAVCs. Some studies were done with speckle tracking analysis of the atria [32, 23]. In conclusion, left atrial EF was acquired through LAVmax and LAVmin obtained from the curve, and the result showed that it remained stable with advancing GA. It resembles the growing pattern of left atrial shortening fraction calculated using the formula: (end-systolic diameter–end-diastolic diameter)/end-systolic diameter, which has been demonstrated to be an alternative parameter for assessing fetal diastolic function [33]. In adults, several studies have found an association between increased ventricular filling pressure and increased LAV and EF, in which changes in its volume correlated with an increase in risk [34–38]. LAV may be more reliable in assessment of diastole than mitral Doppler [39]. It is a stable and reliable parameter that reflects the duration and severity of diastolic dysfunction. The study by Briguori et al. [40] in adults suggested that left ventricular

diastolic function could be better assessed through left atrial motion than through mitral flows in patients with hypertrophic cardiomyopathy. Later a similar study by Zalinski et al. [41] in fetuses of women with diabetes mellitus showed that left atrial shortening was decreased as compared with that in healthy fetuses. Further studies are needed to determine the relationship between LAV and EF and diastolic dysfunction in fetuses in pathological states.

Study limitations

There were several limitations to this study. First, it was a pilot study to apply the LAVT method to determine LAV in normal human fetuses. LAV data obtained through this method lack validation in in-vitro studies or animal experiments. Thus, to approximate the true LAV, more studies are necessary to further assess the accuracy of this method in the future. Second, phasic functions of the left atrium cannot be studied for a lack of guide of the fetal electrocardiogram. Third, there were several limiting factors for TLAVCs acquisition. An important limiting factor was a persistent unfavorable fetal position, which prevented the sonographers from acquiring the standard views, mainly the two-chamber view, which may potentially affect the accuracy of the measurements. Other limiting factors for the acquisition included low image resolution at young GA, abundant fetal movement, and numerous acoustic shadows.

CONCLUSION

This study presents reference ranges for indices of LAV for normal fetuses from 21 to 40 weeks of gestation. The growth curve of LAV of the normal human fetus is in line with that of the left ventricle. In our opinion, more studies are needed to assess to what extent measurements in fetuses in pathological states deviate from normal and whether these measurements can be of use in the prediction of fetal outcomes. Although there are still several factors limiting the application of this method, the LAVT method appears to be a feasible method to estimate fetal LAV and left atrial EF during the second half of gestation, suggesting its potential for assessing left ventricular diastolic function of fetal hearts, especially under pathological conditions in the mother or fetus.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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Clinical factors affecting survival in patients with D-transposition of the great arteries after atrial switch repair: A meta-analysis

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ABSTRACT

Background: Atrial switch repair (AtrSR) was the initial operation method in patients with D-transposition of the great arteries (D-TGA) constituting the right ventricle as a systemic one. Currently, it has been replaced with arterial switch operation (ASO), but the cohort of adults after AtrSR is still large and requires strict cardiological management of late complications. For this reason, we aimed to evaluate potential long-term mortality risk factors in patients with D-TGA after AtrSR (either Mustard or Senning procedures)

Methods: We searched the MEDLINE database for suitable trials. We included 22 retrospective and prospective cohort studies of patients with D-TGA with at least 5 years mean/median follow-up time after Mustard or Senning procedures, with an endpoint of non-sudden cardiac death (n-SCD) and sudden cardiac death (SCD) after at least 30 days following surgery.

Results: A total of 2912 patients were enrolled, of whom 351 met the combined endpoint of n-SCD/SCD. The long-term mortality risk factors were New York Heart Association (NYHA) class ≥III/heart failure hospitalization (odds ratio [OR], 7.25; 95% confidence interval [CI], 2.67–19.7), tricuspid valve regurgitation (OR, 4.64; 95% CI, 1.95–11.05), Mustard procedure (OR, 2.15; 95% CI, 1.37–3.35), complex D-TGA (OR, 2.41; 95% CI, 1.31–4.43), and right ventricular dysfunction (OR, 1.94; 95% CI, 0.99–3.79). Supraventricular arrhythmia (SVT; OR, 2.07; 95% CI, 0.88–4.85) and pacemaker implantation (OR, 2.37; 95% CI, 0.48–11.69) did not affect long-term survival in this group of patients. In an additional analysis, SVT showed a statistically significant impact on SCD (OR, 2.74; 95% CI, 1.36–5.53) but not on n-SCD (OR, 1.5; 95% CI, 0.37–6.0).

Conclusions: This meta-analysis demonstrated that at least moderate tricuspid valve regurgitation, NYHA class ≥III/heart failure hospitalization, right ventricular dysfunction, complex D-TGA, and Mustard procedure are risk factors for long-term mortality in patients after AtrSR.

Key words: atrial switch repair, D-transposition of the great arteries, mustard procedure, senning procedure

INTRODUCTION

D-transposition of the great arteries (D-TGA) is a congenital heart defect characterized by atrioventricular concordance and a lack of arterio-ventricular concordance: the aorta originates from the right ventricle, while the pulmonary trunk originates from the left ventricle [1]. Currently, the surgical treatment of choice for D-TGA is arterial switch operation (ASO). The most common ASO complication, occurring in 8% of patients, is coronary artery obstruction; nevertheless, these patients are also at risk of neo-aortic root dilatation, supravalvular pulmonary stenosis, and left ventricular dysfunction, and ventricular arrhythmias [1, 2]. However, patients after atrial switch repair (AtrSR) using the Senning or Mustard methods still constitute a large group of adult

WHAT'S NEW?

Patients with D-transposition of great arteries (D-TGA) after atrial switch repair (AtrSR) are exposed to long-term sequalae requiring medical care. D-TGA is one of the conditions most prone to sudden cardiac death in congenital heart disease. However, the criteria for implantable cardioverter defibrillator implantation in primary prevention of sudden cardiac death are not clear. We evaluated potential long-term mortality risk factors in patients after AtrSR. We searched the MEDLINE database and analyzed 22 retrospective and prospective cohort studies in this meta-analysis. It showed that at least moderate tricuspid valve regurgitation, New York Heart Association (NYHA) class ≥III/heart failure hospitalization, right ventricular dysfunction, complex D-TGA, and Mustard procedure are risk factors for long-term mortality in patients after AtrSR. To our knowledge, this meta-analysis is the largest in the current literature with the highest number of risk factors for long-term mortality in the operated D-TGA population.

patients, as the 40-year survival rate described in cohorts reaches 60%–75% [3–6]. During AtrSR, the systemic and pulmonary return is redirected with an intra-atrial baffle made of a Goretex patch (Mustard) or native atrial tissue (Senning), thus the right ventricle (RV) becomes systemic. As a consequence of these anatomical alterations, patients are at risk of developing common complications like RV dysfunction or failure, progressive tricuspid valve regurgitation, bradycardia, and chronotropic incompetence, supraventricular and ventricular tachyarrhythmias [1]. According to researchers, complications of AtrSR described as risk factors for non-sudden cardiac death (n-SCD) and/or sudden cardiac death are right ventricular dysfunction (RVD), supraventricular tachyarrhythmias (SVT), tricuspid valve regurgitation (TVR), New York Heart Association (NYHA) class ≥II, and atrioventricular block [3, 7–11]. To our knowledge, this meta-analysis is the largest in the current literature with the highest number of risk factors for long-term mortality in the operated D-TGA population.

Aims

This study aimed to evaluate long-term mortality risk factors in patients with D-TGA after atrial switch operation with either the Mustard or Senning procedure.

Eligibility criteria

We included 22 retrospective and prospective observational cohort studies of patients with D-TGA with at least 5-year mean or median follow-up time after AtrSR either with the Mustard or Senning procedure, with an endpoint of SCD, SCD equivalent events (aborted cardiac arrest or appropriate ICD discharge), or n-SCD after at least 30 days following surgery. The included studies needed to describe mortality and differences between living and deceased patients in the incidence of SVT, RVD, NYHA class, the number of implanted pacemakers, number of patients with simple and complex D-TGA, or number of patients operated with Mustard or Senning procedures.

We included patients with complex D-TGA, i.e. the coexistence of an additional heart defect (ventricular septal defect, pulmonary stenosis, left ventricular outflow tract obstruction, aortic coarctation). Selected studies also reported at least one of the following conditions:

1. SVT including atrial fibrillation and regular atrial tachycardia; RVD as right ventricular ejection fraction <45% assessed by echocardiography were determined by one of the following methods:
   - Simpson apical four-chamber view;
   - Subjective assessment by an experienced cardiologist according to contraction pattern, wall thickness, ventricular dimensions, and septal movement in the presence of significant tricuspid regurgitation and a flow velocity in the ascending aorta of less than 0.7 m/sec.;
   - Partial subjective assessment, with right ventricular size and function assessed utilizing tissue Doppler imaging and tricuspid annular plane systolic excursion (TAPSE);
2. Functional NYHA class ≥III or hospitalization for heart failure (HF);
3. Atrioventricular block, sick sinus syndrome, or arrhythmia requiring pacemaker implantation; at least moderate TVR, assessed in Doppler echocardiography by an experienced cardiologist or catheterization with angiography;
4. Comparison of the number of patients operated with Mustard and Senning procedure.

Studies with no estimates of the association between risk factors and survival were excluded. We excluded studies that focused on specific subgroups of patients with D-TGA e.g., pregnant women, studies including D-TGA with other complex heart defects e.g., tetralogy of Fallot, and patients after double-switch surgery. Other exclusion criteria were studied groups <5 patients, language of the manuscript other than English, and other studies from the same research site describing the same cohort again.

Study process and search strategy

We investigated the MEDLINE database from its inception date to April 30, 2021 to find cohort studies describing long-term mortality and/or SCD risk factors in patients with D-TGA after atrial switch repair. While searching for suitable abstracts, we did not establish any language restrictions or filters. The search terms we used were (transposition of the great arteries OR TGA OR dTGA OR cTGA OR cctg OR systematic right ventricle OR atrial switch OR arterial switch

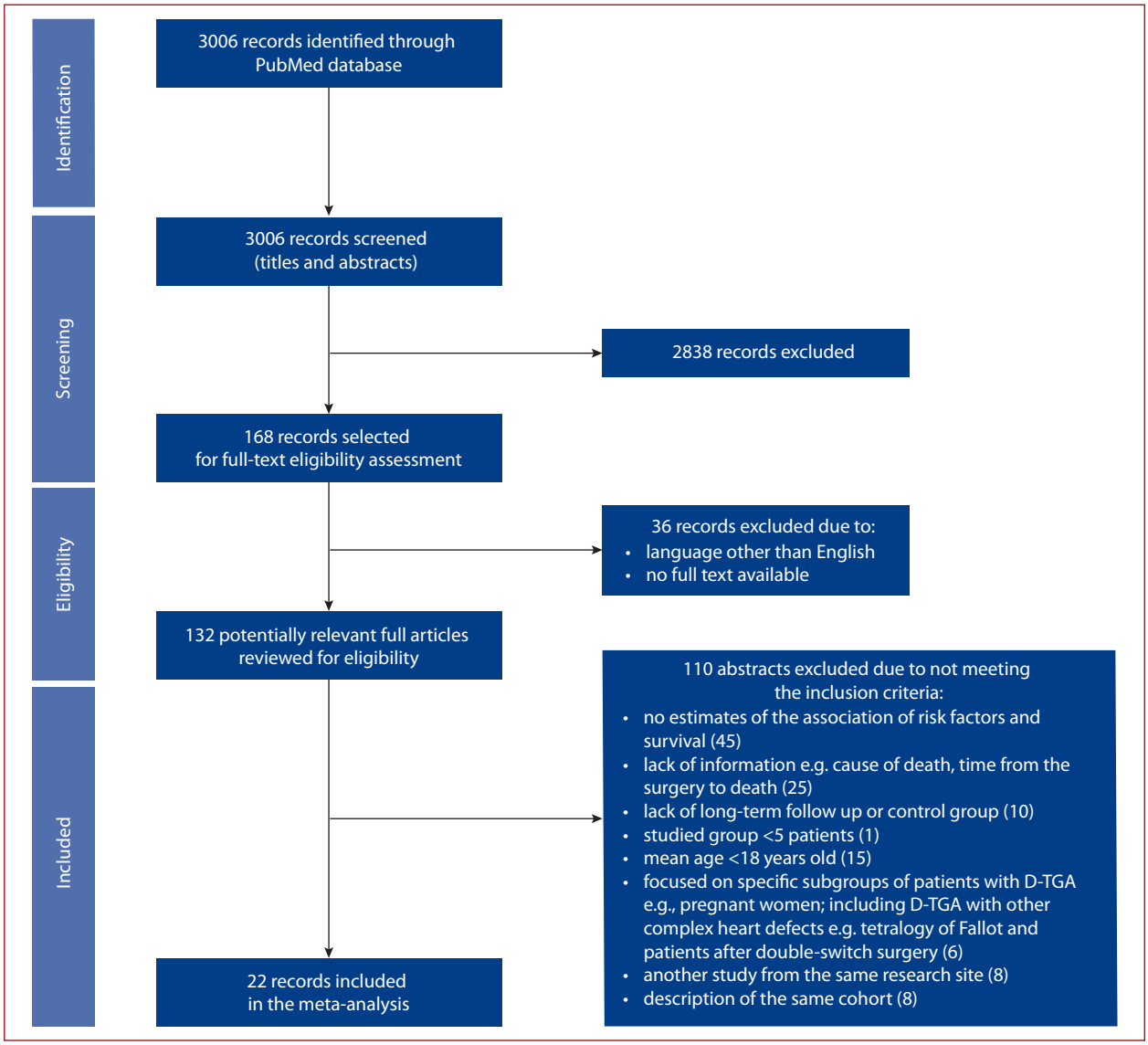

Figure 1. The study flowchart

Abbreviations: D-TGA, D-transposition of the great arteries

OR mustard procedure OR senning procedure) AND (death OR sudden death OR cardiac death OR sudden cardiac death OR outcome OR prognosis OR risk factors) AND (adults OR adolescents). One investigator (SN) analyzed the entire database searching for suitable articles and simultaneously excluded duplicates, from which 168 articles were selected for full-text eligibility assessment (Figure 1). After 36 records were excluded due to language other than English and no full-text availability, two investigators (SN and EJ) reviewed 132 potentially relevant full articles. Finally, we excluded 110 manuscripts for the reasons listed in Figure 1. Eventually, 22 records met the inclusion criteria. Additionally, we verified the references of the included articles in search of potential new studies. The studies included in the analysis were approved by an appropriate institutional review board or ethics committee and patients provided written informed consent to participate in the study. All extracted relevant information was double-checked by the investigators. Other team members (AC, PR, SG, ML, OT) were responsible for substantive oversight and resolving uncertain decisions.

Data extraction and quality assessment

The quality of the included studies was assessed by two reviewers (EJ and SN) with the use of the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Supplementary material, *Table S1*) [12]. We checked if the information about study patient loss, their number, and reasons for exclusion (including the safety outcome data) was provided. We extracted data describing study characteristics such as country, study design, length of follow-up, number of patients in each research group, and number of study sites. The patient population characteristics included age, percentage of females and males, mean or median follow-up time, and percentage of patients with complex D-TGA, sinus node dysfunction, baffle obstruction, and in need of reintervention or pacemaker implantation. We also

considered the numbers of n-SCD, SCD, aborted cardiac arrests, and appropriate ICDs.

Statistical analysis

The included research data were meta-analyzed using Review Manager 5.4. The random-effects model and inverse variance method were used to estimate the odds ratio (OR) of the combined endpoint of n-SCD, SCD, or SCD equivalent events. A total of 22 retrospective or prospective observational cohort studies were included in this meta-analysis [7–9, 11, 13–30]. There were seven main comparisons, which included: (1) NYHA functional class ≤II vs. NYHA ≥III/HF hospitalization [9, 11, 26]; (2) TVR <moderate vs. ≥moderate [8, 9, 11, 13, 16, 20, 21, 28, 31]; (3) Mustard vs. Senning procedure [7–9, 11, 14, 19, 20, 22, 28]; (4) complex vs. simple D-TGA [8, 9, 13, 16, 20, 21, 24, 27–29, 31]; (5) RVD vs. no RVD [8, 9, 11, 13, 15, 16, 18–23, 28]; (6) history of SVT vs. no history of SVT [7, 9, 13, 14, 16, 19, 21, 23, 27, 28, 30, 31]; (7) pacemaker vs. no pacemaker implantation [8, 9, 11, 16, 21, 23, 30]. The secondary endpoint was defined as SCD or SCD equivalent events and the random-effects model and inverse variance method were used to estimate the OR. The *P*-value <0.05 was considered as statistically significant.

The χ^2 test was used to assess the significance of heterogeneity between the results of different research and presented as the I^2 test. Significant heterogeneity was defined as I^2 >50%, and I^2 <25% was defined as non-significant heterogeneity [32].

RESULTS

Study characteristics

The included studies examined a total of 3067 patients, 73 of whom were lost to follow-up and 82 died within 30 days of the atrial switch repair. A total of 2912 patients were finally enrolled, of whom 351 met the combined endpoint of n-SCD, SCD, or SCD equivalent events. Twenty of included studies were single-center types from sites in 12 countries [7, 9, 11, 13–19, 21–24, 26–31]. The remaining 2 studies were multi-center international studies with 2 to 3 involved countries and 7 clinical sites each [8, 20]. In the described research groups, the average age ranged from 13.9 to 35 years, and men accounted for 51.3%–89.2%, with an average follow-up time from AtrSR of 9.9–30 years. The mean age at the time of AtrSR ranged from 6.9 to 46 months; 1321 patients were operated on by the Mustard method and 1340 by the Senning method; 251 cases were described as AtrSR without exact numbers on the procedure method. The proportion of patients with the D-TGA complex ranged from 0% to 49.4%, with one study also including one patient representing 1% of the study population with the Taussig-Bing anomaly [26]. Of 351 deaths, 142 (40.4%) were n-SCD, 194 (55.3%) were SCD, and 15 (4.3%) were SCD-equivalent events. The characteristics of the included studies are summarized in Supplementary material, *Table S2*.

Meta-analysis

A meta-analysis of the reported risk factors was performed (Figure 2A–B). Data on RVD was available from the highest number of publications (13 articles with a total number of 1489 patients); data on procedure type in 8 articles with 1348 patients; data on SVT in 12 articles with a total number of patients equaled 1339; complex vs. simple D-TGA was evaluated in 11 articles with 1257 patients; at least moderate TVR in 9 articles with 870 patients; implantation of pacemaker in 5 articles with 526 patients; NYHA class ≥III/HF hospitalization in 3 articles with 251 patients (Table 1).

A statistically significant relationship was found between at least moderate NYHA class ≥III HF hospitalization (*P* <0.001), TVR (*P* <0.001), type of surgical procedure (*P* <0.001), complex D-TGA (*P* = 0.005), and the combined endpoint of n-SCD, SCD, and SCD-equivalent events. We observed an association of borderline statistical significance between RVD (*P* = 0.05) and the primary endpoint. We did not observe statistically a significant (*P* = 0.09) relationship between SVT or pacemaker implantation (*P* = 0.29) and the primary endpoint (Figure 2A–B). We performed an additional analysis in which we assessed SVT separately for n-SCD and SCD/SCD equivalent events (Figure 3) [33]. The meta-analysis showed that SVT is associated with SCD (odds ratio [OR], 2.74; 95% confidence interval [CI], 1.36–5.53; *P* = 0.005). To confirm that SVT is a risk factor for SCD, we performed a separate meta-analysis for SVT as an n-SCD risk factor (Figure 3). We did not find a significant (OR, 1.5; 95% CI, 0.37–6.0; *P* = 0.57) relationship between SVT and n-SCD, which confirms that SVT is a risk factor only for SCD.

The overall heterogenity of particular analysis was considered significant for RVD (I^2 = 60%), SVT (I^2 = 53%) and pacemaker implantation (I^2 = 68%). The analysis of NYHA class ≥III/HF hospitalization (I^2 = 0%), and type of procedure (I^2 = 18%) had non-significant heterogeneity. The analysis for at least moderate TVR (I^2 = 49%) and complex D-TGA (I^2 = 48%) showed intermediate heterogeneity.

DISCUSSION

This meta-analysis demonstrated that at least moderate tricuspid valve regurgitation, NYHA class ≥III/heart failure hospitalization, right ventricular dysfunction, complex D-TGA, and the Mustard procedure are risk factors for long-term mortality in patients after AtrSR.

NYHA class

NYHA functional class appeared to be a significant risk factor for the combined endpoint of long-term mortality. Since assessment of right ventricular dysfunction by echocardiography is not standardized, we decided to evaluate the clinical status of patients with the use of

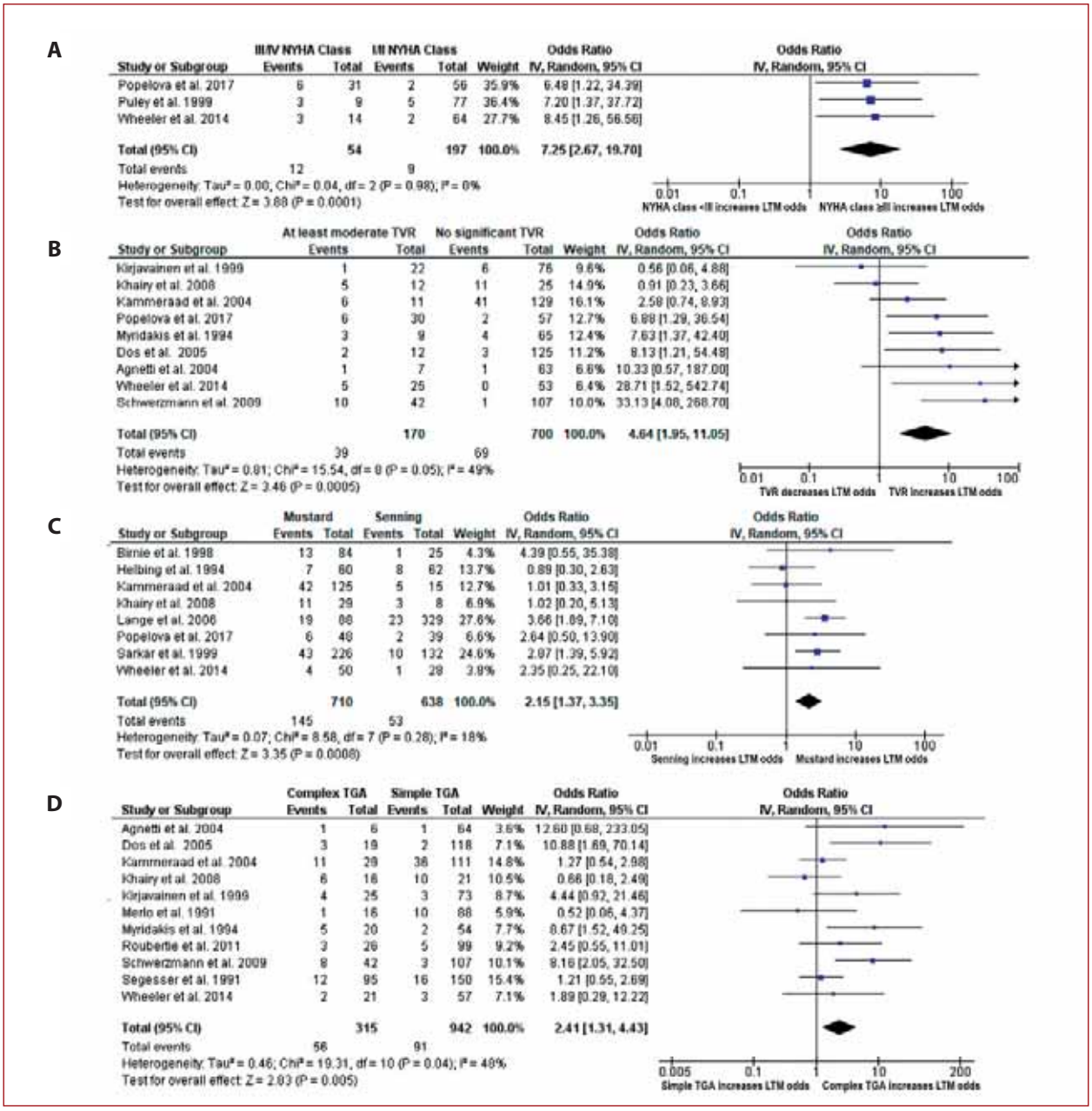

Figure 2A. Forest plots showing pooled odds ratios of NYHA >II/heart hospitalization (**A**), at least moderate TVR (**B**), Mustard procedure (**C**), Complex D-TGA (**D**). D-TGA indicates D-transposition of the great arteries

Abbreviations: D-TGA, D-transposition of great arteries; NYHA, New York Heart Association; LTM, long-term mortality;TVR, tricuspid valve regurgitation

NYHA class/HF hospitalization as a risk factor for death in patients after AtrSR. Although recent guidelines do not recommend to use the NYHA functional status in adults with congenital heart defects, this parameter has been used in numerous older publications on the survival in this group of patients [1]. Most of the patients with NYHA class I and II function are well adapted and report no clinical symptoms like dyspnea despite the objectively reduced exercise capacity in cardiopulmonary tests [11, 34]. Of the 251 patients included in the studies comparing NYHA class/HF hospitalization in living and deceased patients, as many as 54 (21.5%) patients were hospitalized for HF or were in the functional NYHA class ≥III. Previous articles, which did not show the relationship between the NYHA class and mortality, did not involve in the analysis a more objective tool, which is hospitalization for heart failure [11, 34]. In our study, clinical deterioration related to systemic ventricular dysfunction turned out to be a significant risk factor for death, which confirms that NYHA class ≥III/HF hospitalization reflects the disturbance of temporal RV compensation. Popelova et al. [11] showed a correlation between N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration and mortality, while not showing a statistically significant relationship be-

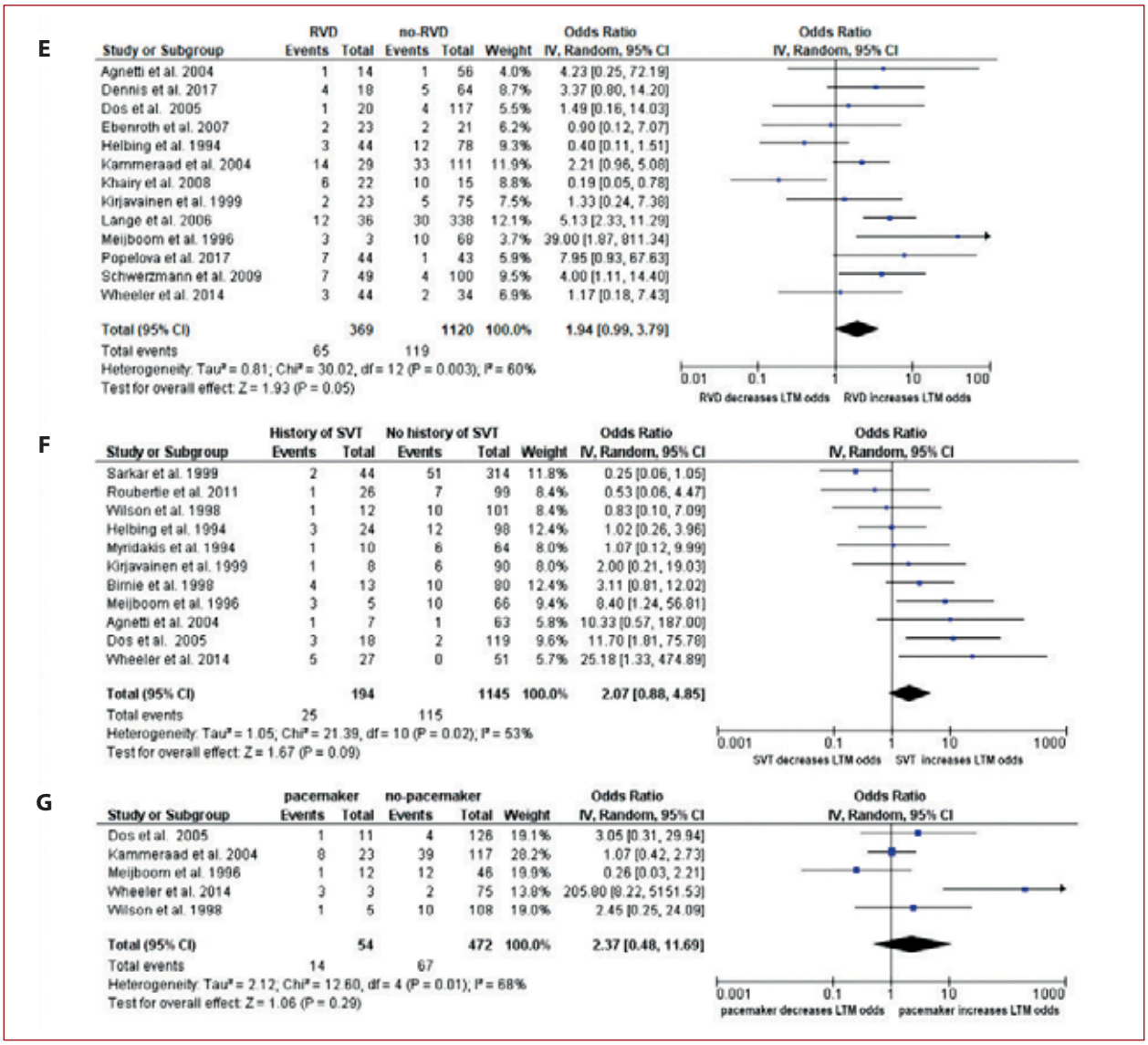

Figure 2B. Forest plots showing pooled odds ratios of RVD (**E**), history of SVT (**F**), and pacemaker implantation (**G**) for long-term mortality using a random effects meta-analysis approach

Abbreviations: RVD, indicates right ventricular dysfunction; SVT, supraventricular tachyarrhythmia

Table 1. Summary of pooled odds ratios results in the random-effect model

Comparison	Odds ratio	95% CI	*P*-value
NYHA functional class ≥III/HF hospitalization vs. NYHA Class ≤II	7.25	2.67–19.7	<0.001
At least moderate TVR vs. no TVR	4.64	1.95–11.05	<0.001
Mustard vs. Senning procedure	2.15	1.37–3.35	<0.001
Complex vs. simple D-TGA	2.41	1.31–4.43	0.005
RVD vs. no RVD	1.94	0.99–3.79	0.05
History of SVT vs. no history of SVT	2.07	0.88–4.85	0.09
Pacemaker vs. no pacemaker	2.37	0.48–11.69	0.29

Abbreviations: CI, confidence interval; HF, heart failure; other — see Figure 2

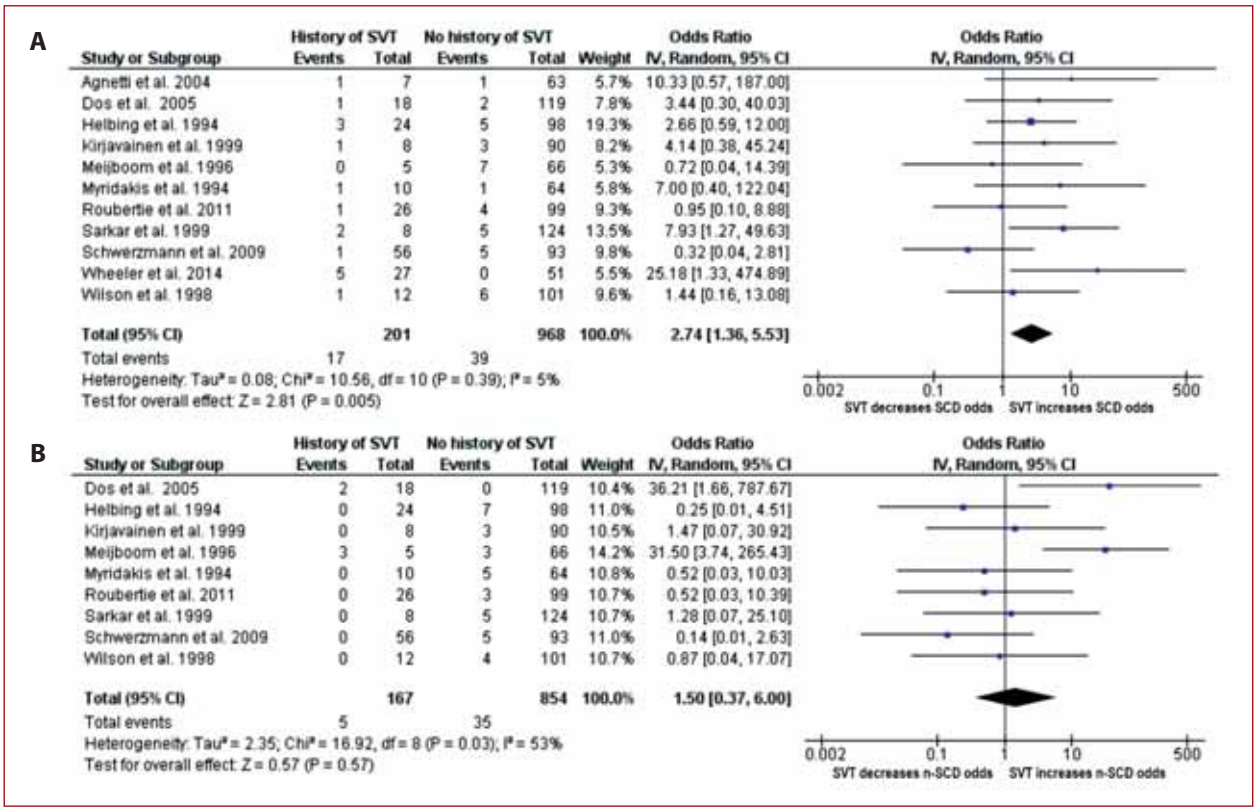

Figure 3. Forest plots showing pooled odds ratios of SVT for SCD (**A**) and n-SCD (**B**) using a random effects meta-analysis approach. n-SCD indicates non-sudden cardiac death

Abbreviations: SCD, sudden cardiac death; other — see Figure 2

tween the NYHA class and mortality. This may suggest that a combination of NT-proBNP and hospitalization for heart failure might be a more sensitive tool in assessing the clinical status and risk of death in patients after AtrSR.

Tricuspid valve regurgitation

Tricuspid valve regurgitation turned out to be the strongest risk factor for death in our review. The systematic tricuspid valve becomes progressively incompetent in patients with operated D-TGA. In most cases, TVR results from ring dilatation caused by enlargement of the failing systemic RV, but occasionally it can also be caused by surgical injury [35]. TVR is often commensurate with RVD, but it is not a constant or linear relationship as severe TVR does not develop in all patients with dysfunctional RV. The results on the use of TVR severity as an indirect parameter in assessing systematic ventricular impairment are contradictory [36, 37]. However, TV replacement/repair surgery showed stabilization of RV function and improvement of NYHA functional class [38]. In addition, TVR severity has been shown to correlate with exercise capacity of these patients assessed in cardiopulmonary tests [39]. The severity of TVR may not necessarily correspond to RVD, but it has a significant impact on the clinical status of patients with corrected D-TGA and is therefore a significant risk factor for death in this group.

Right ventricular dysfunction

To date, cohort studies have shown a statistically significant association between RVD and long-term mortality [15, 18, 21, 40]. Our meta-analysis has shown that there is a statistical tendency between RVD and long-term mortality in patients with operated D-TGA. However, a previous review article by Venkatesh et al. [33] did not confirm such results. The difference between the outcomes may be due to the discrepancy between exercise capacity, symptomatic HF, and RVD subjectively assessed by echocardiography [16, 19, 24, 41]. Additionally, systemic failure of the right ventricle due to its triangular structure and different orientation of myocardial fibers seems to have a significant diastolic component [36]. Due to this fact and the RV volume and its mechanism of adaptation to systemic load, echocardiographic assessment of RV systolic function does not always have to deteriorate. It seems that RVD evaluated by cardiac magnetic resonance will be a more reliable measure. However, the current studies, surprisingly, do not show an association between CMR parameters and patients' clinical status or exercise capacity with corrected D-TGA [42, 43].

Surgery procedure type

Mustard surgery proved to be a significant risk factor for death compared to the Senning procedure, which is in line

with the previous publications [7, 22, 33]. The use of artificial material to create baffles requires more sutures lines within the atria, poses a higher risk of baffle obstruction and thus the risk of reoperation. The articles we included were published between 1991 and 2017 reflect different surgical experiences, quality of extracorporeal circulation technology, hypothermia, use of cardioplegia, and perioperative care. All those factors could impact long-term results in this group. Right after introduction of the Mustard procedure, patients were operated on without the use of cardioplegia and cardioprotection, which also could have impacted outcomes. In the current era, the treatment of choice is arterial switch operation, but too few available data prevented us from comparing long-term mortality between AtrSR and ASO subgroups.

Complexity

The complexity of the defect turned out to be an important risk factor for the combined endpoint of long-term mortality. This can be related to the greater extent of anatomical abnormalities subsequently requiring a more extensive surgical repair, which prominently translates into worse clinical conditions. Moreover, chronic hypoxia associated with delayed AtrSR can cause myocardial ischemia and scarring. A greater extent of the surgical procedure may contribute to the excessive scar formation predisposing to iatrogenic right bundle branch block. It may also predispose to the subsequent SVT and RVD [3, 22]. The lack of a unified definition of complex TGA among the included studies may bias the outcomes of our meta-analysis. Still, previous research also described the complexity of TGA as a risk factor for death [31, 33].

Supraventricular tachyarrhythmia

We have not shown that SVT is a risk factor for the combined endpoint consisting of n-SCD and SCD with equivalent events. Since previous investigators showed such an association [33], we performed a separate analysis of SVT as a risk factor for SCD that showed a statistically significant relationship between them [33]. Additionally, the analysis of SVT as an n-SCD risk factor did not confirm such a relationship. The most common SVT occurring in patients after D-TGA correction is a cavo-tricuspid isthmus-dependent flutter, followed by a macro-reentry circuit related to surgical scars. The incidence of SVT increases with aging and affects up to a third of these patients [36, 44], with atrial fibrillation typically occurring at older age [1]. Due to the presence of stiff baffles impairing the capability to increase the preload, the high heart rate is poorly tolerated hemodynamically and can be fatal [1]. In addition, SVT may contribute to SCD with 1:1 conduction through the healthy atrial node but also because of potential ischemia of the systemic ventricle supplied by only one coronary vessel which is the right coronary artery [13, 16]. Cohort studies showed a significant statistical relationship between SVT and SCD and a poor relationship between tachyarrhythmias and overall mortality [7, 16]. Our meta-analysis confirmed these findings. However, even if SVT was found to be related only to SCD and not to the combined endpoint, it is worth emphasizing that arrhythmia may be a surrogate marker for dysfunctional systemic ventricles and indirectly may also lead to n-SCD [45].

Pacemaker

Pacemaker implantation did not show a statistically significant relationship with long-term mortality in patients after AtrSR. Due to altered heart anatomy and frequent secondary atrioventricular conduction disturbances, we assumed that this might have an impact on survival in patients with corrected D-TGA [3, 30, 46]. However, similarly to other authors, implantation of a pacemaker was not a statistically significant predictive risk factor for death [11, 30, 47]. This finding confirms that pacemaker therapy is an effective treatment for various conduction system disorders.

Study limitations

The studies included in this meta-analysis are characterized by large discrepancies in the era and quality of medical services, such as cardiac surgery, extracorporeal circulation, or postoperative care. In addition, not all studies used cardioplegia, and patients differed in comorbidities and socioeconomic conditions. This results in a very high heterogeneity of the studies included in this meta-analysis. As these were mainly retrospective studies, it should be underlined that all of them differed in study design, risk factor definitions, and endpoints. We were unable to produce a unified definition for the D-TGA complex. Additionally, we also adopted an RVEF cutoff point of <45% as a criterion for RVD, though the majority of publications defined RVD as RVEF <40%. Importantly, the rated and analyzed outcomes parameters, such as TVR, RVD, or NYHA class, were based on our subjective judgment and clinical experience. No prospective screening with echocardiography, electrocardiography, or other modality was performed, and the outcomes may be incorrectly estimated. In our opinion, the results describing the outcomes, such as right ventricular dysfunction or tricuspid valve regurgitation, may have the largest error because of our subjective assessment. Lastly, as the risk factors included in our study are derived from univariate analyses, the multicollinearity between them may occur, which should be kept in mind in clinical practice.

CONCLUSIONS

Heart failure decompensation and at least moderate tricuspid valve regurgitation have the biggest impact on long-term survival in patients after the atrial switch procedure for D-transposition of the great arteries. Right ventricular dysfunction, the complexity of the congenital heart defect, and Mustard procedure are also risk factors for mortality in

these patients. Supraventricular tachyarrhythmia is a risk factor for sudden cardiac death but does not affect all-cause mortality in this group.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

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Relationship between left main trifurcation angulation, calcium score, and the onset of plaque formation

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ABSTRACT

Background: It has been suggested that a wider left main (LM) bifurcation angle is associated with the development of atherosclerosis. However, the relationship between LM trifurcation angulation and atherosclerosis has not been investigated.

Aims: We aimed to investigate the relationship between LM trifurcation angulation and the presence of calcifications in the left coronary artery (LCA) using coronary computed tomography angiography (CCTA). Furthermore, we assessed the relationship between LM trifurcation angulation and the age at which calcification originated.

Methods: The LM trifurcation angle and coronary artery calcium (CAC) score in the LCA were measured. Based on observational studies, we assumed that CAC progression is 25% per year on average. Then, we calculated the age at which LCA CAC scores were lower than 0.1 Agatston units.

Results: Of 266 patients, 52 patients (mean age of [standard deviation, SD] 61 [6] years; 28 men) with LM trifurcation were included in the study. Calcified plaques occurred in the LCA in 36 patients (69.2%). The mean LM trifurcation angle in patients with a diseased LCA was wider than that in patients with a normal LCA (108° [33°] vs. 91° [28°]; $P = 0.04$). Pearson correlation coefficient showed that the wider the LM trifurcation angle was, the earlier the calcification in the LCA may be expected ($r = –0.34$; $P = 0.04$ with outliers; $r = –0.43$; $P = 0.009$ without outliers).

Conclusions: A wider LM trifurcation angle is associated with a higher LCA CAC score. Moreover, the LM trifurcation angle has a significant impact on the earlier onset of atherosclerosis.

Key words: coronary atherosclerosis, coronary computed tomography angiography, calcium score, left main trifurcation angulation

INTRODUCTION

Despite the exposure of the coronary arteries to systemic risk factors, the distribution of atherosclerotic plaques is focal and forms at specific precisely defined risk points. Typical locations are proximal segments of coronary artery branches and inner curvatures, areas of flow recirculation and flow reversal where wall shear stress is on average low and fluctuates during the cardiac cycle [1–4].

Computed tomography allows visualization of coronary artery plaque distribution and assessment of a coronary calcium score. Coronary artery calcium (CAC) score is an independent and powerful predictor of coronary artery diseases [5]. It has been shown that a wider bifurcation angle between the left anterior descending (LAD) and left circumflex branch (LCx) is associated with the development of coronary atherosclerosis [6–13].

However, the relationship between left main (LM) trifurcation angulation and atherosclerosis is unknown. This study aimed to investigate the relationship between LM trifurcation angulation, plaque burden reflected by the CAC score, and the onset of plaque formation.

WHAT'S NEW?

For the first time, the relationship between left main (LM) trifurcation angulation and atherosclerosis was investigated. In our study, a wider left coronary artery trifurcation angle was associated with a higher coronary calcium score in the left coronary artery. We also found that the LM trifurcation angle is a geometric risk factor for atherosclerosis and has a significant impact on the onset of coronary calcification. Local hemodynamic factors may be the major determinants of atherosclerotic plaque localization and progression.

METHODS

Study population

The Bioethics Committee granted an exemption from ethics approval for this study. In addition, the need for informed consent from study participants was waived. This study was an observational retrospective registry of individuals who underwent CAC scoring as part of health check-ups in a self-referral setting.

Of the 266 consecutive patients with suspected chronic coronary syndrome with an intermediate or a low probability of coronary artery disease undergoing coronary computed tomography angiography (CCTA) at the Silesian Center for Heart Diseases over a period of one year, 52 patients 61 (6) years; 28 men with LM trifurcation were included in the study. Patients included in the study had no other vascular abnormalities on CCTA. Patients with stents and pacemakers and those who had myocardial infarction, percutaneous transluminal coronary angioplasty, or coronary bypass surgery were excluded.

The evaluated risk factors for coronary artery disease were hypertension (systolic blood pressure values of at least 140 mm Hg and/or diastolic blood pressure values of at least 90 mm Hg or taking antihypertensive drugs), diabetes mellitus (fasting plasma glucose level ≥7.0 mmol/l, 2-hour plasma glucose ≥11.1 mmol/l, random plasma glucose ≥11.1 mmol/l with symptoms or use of oral antidiabetic therapy and insulin), smoking (active smokers), positive family history of coronary artery diseases (in first-degree male relatives before 55 years of age or female relatives before 65 years of age), body mass index and hypercholesterolemia (low-density lipoprotein cholesterol level of at least 3 mmol/l).

CCTA protocol

CCTA scans were performed using a 128-slice dual-source computed tomography scanner (SOMATOM Definition Flash, Siemens Healthineers, Forchheim, Germany). First, non-contrast computed tomography scans were performed to evaluate the CAC score. Then, the nonionic low osmolar contrast agent Omnipaque 350 mgI/ml (Iohexol, GE Healthcare, Chicago, IL, US) was injected to visualize the coronary arteries (average 55 ml of contrast per patient with a flow of 5–5.5 ml/sec). The scanning parameters were beam collimation 2 × 64 mm × 0.6 mm with a z-axis flying spot, slice thickness of 1.5 mm, tube voltage ranging from 100 to 120 kV (depending on body mass index [BMI]), tube current of 300–450 mA, and reconstruction interval of 0.5 mm with electrocardiogram gating. All patients were given a 0.8 mg dose of nitroglycerin lingual spray, and patients with a heart rate above 75 beats per minute were given 2.5–5 mg intravenous metoprolol.

Measurement of calcium score and left main trifurcation angle

The CAC score was calculated by the Agatston method. The presence of a lesion with an area greater than 1 mm^2 and a peak intensity greater than 130 Hounsfield units was automatically identified and color-coded by the software (Syngo.via). Calcium scores of the LM, LAD, intermediate artery (IM), and LCx were summed to calculate the total left coronary artery (LCA) calcium score.

The LM trifurcation angle was calculated after identifying the centerline vectors along the course of the LAD and LCx. The LM trifurcation angles were measured in diastole based on multiplanar reconstructions (MPR) views.

Figure 1 shows a schematic measurement of the LM trifurcation angle. The angle between the LAD and LCx was measured independently by two readers with over 15 years of clinical and research experience in cardiac computed

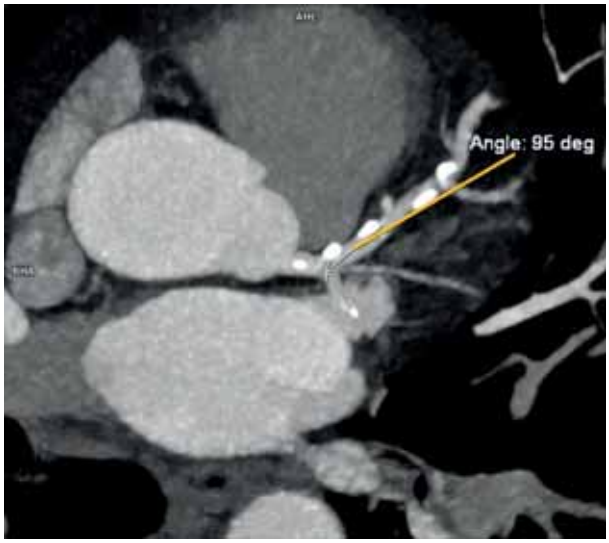

Figure 1. Measurement of the left main (LM) trifurcation angle. The angle between the left anterior descending artery (LAD) and left circumflex (LCx) branch is 95°. Calcified plaques are present at the LM, LAD, and LCx

Table 1. Baseline characteristics of the study population

Risk factors	Whole population (n = 52)	CAC = 0 (n = 16)	CAC >0 (n = 36)	*P*-value
Age, years, mean (SD)	61 (6)	58 (9)	63 (8)	0.07
Male sex, n (%)	28 (54)	7 (44)	21 (58)	0.33
Body mass index, kg/m^2, mean (SD)	27.7 (3)	27 (3)	28 (3)	0.32
Hypertension, n (%)	28 (54)	9 (56)	19 (53)	0.82
Type 2 diabetes mellitus, n (%)	5 (9.6)	2 (12)	3 (8)	0.64
Current smoker, n (%)	9 (17.3)	4 (25)	5 (14)	0.33
Family history of CAD, n (%)	16 (30.8)	7 (44)	9 (25)	0.18
Hypercholesterolemia, n (%)	15 (28.8)	7 (44)	8 (22)	0.11
eGFR (Cockcroft-Gault), ml/min/1.73 m^2, median (IQR)	95 (84–95)	95 (84–96)	94 (84–95)	0.07

Abbreviations: CAD, coronary artery disease; eGFR, estimated glomerular filtration rate

tomography. Three measurements were obtained, and the average values were analyzed.

Statistical analysis

Quantitative data are reported as mean (standard deviation [SD]) or median with interquartile ranges (IQR). Qualitative data are expressed as counts and frequencies. Qualitative variables were compared using the χ^2 test. The Mann-Whitney U-test was used to compare continuous variables with a distribution other than normal. Depending on the value of the calcification score, patients were divided into two groups: with calcifications (CAC >0) and without calcifications (CAC = 0) in the LCA. The Shapiro-Wilk test was used to check the normality of the data in a given group. Homoscedasticity was assessed by the mean-based Levene test. The differences between LM angles in the groups were tested using a one-tailed t-test.

In addition, the likelihood of calcification occurrence with increasing LM trifurcation angle was calculated. To assess the exact change in the odds, univariable logistic regression was performed.

Furthermore, we investigated the influence of the LM trifurcation angulation on the onset of calcification in relation to age using Pearson correlation. To do so, for each patient, we estimated the age at which the disease originated. According to the literature, we assumed that CAC is progressing at an average of 25% per year [14–16], and then we calculated the age at which the CAC score in the LCA was less than 0.1 Agatston units in each patient.

P-values <0.05 were considered statistically significant. Statistical analysis was performed using the Python package (numPy, sciPy, statsmodels, scikit-learn).

RESULTS

The final study group consisted of 52 patients. The median age of the study population was 61 (6) years; 54% of the patients were male. A similar proportion of patients in the subgroup had hypertension and type 2 diabetes mellitus. All patients suffering from hypercholesterolemia had been taking statins. The demographic and clinical characteristics of the patients are presented in Table 1. Calcifications were found in the LCA in 36 patients (69.2%) in the study group. Patients with CAC >0 had, on average, a wider LM trifurcation angle than patients without calcifications (*P* = 0.04). The mean LM trifurcation angle was 108° (33°) in patients with CAC >0, which was considerably wider than the angle measured in patients with CAC of 0, which was 91° (28°) (Supplementary material, *Figure S1*).

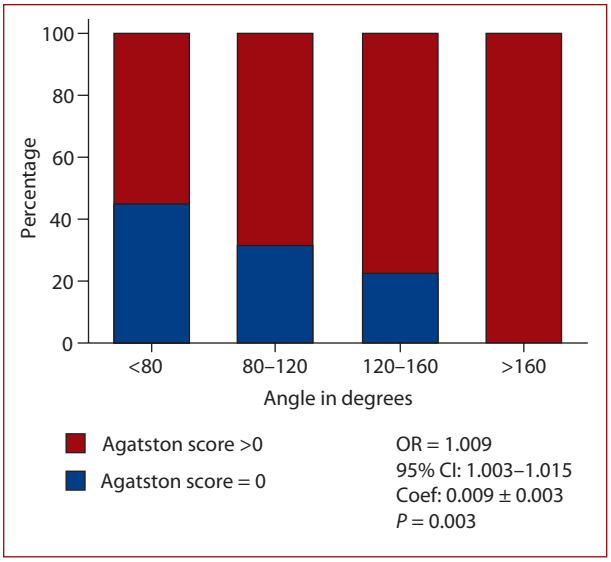

Figure 2. Logistic regression results. The histogram presents that a wider left main trifurcation angle is associated with an increase in the odds of calcifications in the left coronary artery

Abbreviations: CI, confidence interval; OR, odds ratio

We also assessed changes in the likelihood of calcification occurrence with an increase in the LM trifurcation angle. The histogram plotted in Figure 2 shows that wider angulation is associated with an increase in the odds of LCA calcification. In the logistic regression analysis, LM trifurcation angles were predictors of occurrence of lesions in the LCA, and each degree of increase in the LM angle comes with approximately 1% greater odds of occurrence of calcification in the LCA (odds ratio [OR], 1.009; 95% confidence interval [CI], 1.003–1.015; *P* = 0.003).

Then, the age at which calcifications originated was correlated with LM trifurcation angulation (Figure 3). Among the plotted points, one subject was assessed as an outlier and marked with a red color. This was an extreme obser-

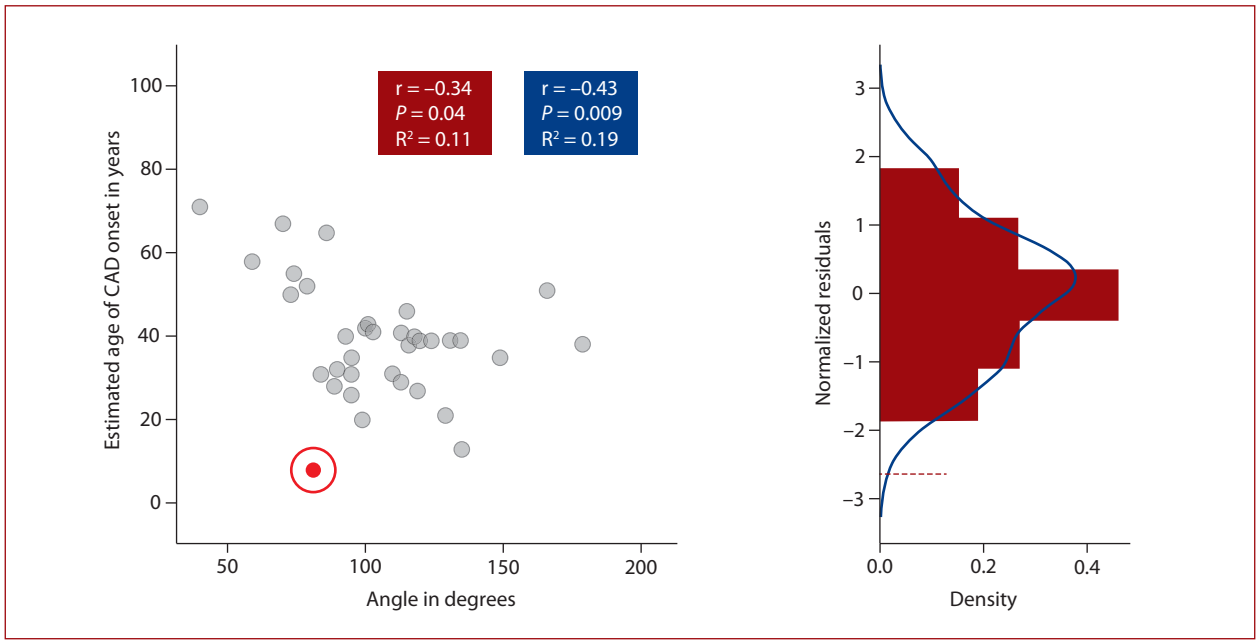

Figure 3. Pearson correlation results. On the left side, the relationship between the left main trifurcation angle and the age at which the left coronary artery calcium score was lower than 0.1 Agatston units in each patient. One subject was assessed as an outlier and marked with a red color. Two correlation coefficients were calculated: one considering the outlier (the red color) and one excluding the outlier (blue color). Both results were statistically significant. On the right side, the plot of normalized residuals. The residual calculated for the outlier differs by nearly 3 standard deviations from the expected value of this distribution, so we decided to treat this point as a potential outlier

Abbreviations: see Table 1

vation, possibly disrupted by additional risk factors. Two correlation coefficients were calculated: one considering the outlier (red color) and one excluding the outlier (blue color). Both results were statistically significant (r = –0.34; $P = 0.04$ vs. r = –0.43; $P = 0.009$, respectively) and indicate that the wider the LM trifurcation angle is, the earlier calcification may be expected in a given patient.

The diameters and lengths of each main branch artery did not influence the distribution and severity of coronary artery calcification (results were not included in the publication).

DISCUSSION

Approximately 20%–38% of the population has LM trifurcation [17–20]; however, the relation between LM trifurcation angulation and atherosclerosis is unknown. For the first time, the relationship between LM trifurcation angulation and atherosclerosis was investigated in this study. We found that the LM trifurcation angle is a geometric risk factor for atherosclerosis and has a significant impact on the onset of coronary calcification. The patients with trifurcation of the LM and a CAC score above 0 had a wider LAD and LCx angle than the patients with CAC of 0. Moreover, a larger angle between side branches is associated with an increase in the odds of calcification occurrence. Finally, we demonstrated for the first time that the wider the LM trifurcation angle is, the earlier the onset of calcification is expected. This observation suggests that plaque formation and coronary artery calcification are related to arterial geometry features and local shear stress distribution. The presence of an intermediate branch requires a wider LM angle. This geometry of arteries promotes secondary disturbed flows that generate regions of low and/or oscillatory wall shear stress at the lateral wall of the LM divider [21]. Low and/or oscillatory endothelial shear stress induced by mechanotransduction changes the proatherogenic phenotype of endothelial cells [22]. We believe that measuring the LM trifurcation angle in patients without lesions in the LCA may be prognostic.

Our results are in line with observations focused on LM bifurcation [6–13, 23]. All of them demonstrated that LAD-LCx bifurcation angulation is a potential geometric risk factor for atherosclerosis. For instance, Cui et al. [6] suggested that a wider bifurcation angle between the LAD and LCx is associated with noncalcified lesions and might predict significant left coronary stenosis. Interestingly, Sun et al. [7, 13, 24] demonstrated that the measurement of the LM bifurcation angle improves the diagnosis of calcified plaques. According to Ziyrk et al. [25], the bifurcation angle has an impact on the localization of lesions.

Another study focuses on LM-LAD angulation. Moon et al. [8] showed that a wider LM-LAD angle could be used to identify patients at higher risk for coronary artery disease. Konishi et al. [26] studied the relationship between LM and LAD angulation in a population with chronic kidney disease and reported that a wider LM-LAD bifurcation angle was associated with a high CAC score. Furthermore, Konishi et al. [27], in another study, postulated that a wide LM-LAD angle was a predictor of restenosis after stent implantation in proximal LAD disease. Malvè et al. [20], using computational fluid dynamics simulations, showed that the tortuosity of

the LM-LAD coronary branches is associated with low wall shear stress and could be used as a surrogate marker for the onset of atherosclerosis. Other authors also postulated that a wide angle between side branches intensifies disturbed blood flow, magnitude of reversed flow, and flow separation, increasing the spatial wall shear stress variations that are important in atherogenesis [28–30].

The present study has some limitations that should be pointed out. First, we considered only calcified plaques. Notably, the CAC score represents the progression of both the noncalcified and calcified plaque burdens in patients without statin use [31]. Second, there was no correlation with invasive coronary angiography. Notably, however, according to Sun and Chaichan, there is no difference between angle measurements on CCTA and invasive angiography [32]. Third, we did not adjust for confounding risk factors for CAC. In our study, the patient populations with CAC of 0 and CAC greater than 0 were homogeneous. In addition, patients with high CAC scores without traditional risk factors have an increased incidence of coronary heart disease events, whereas patients without CAC with multiple risk factors have a low event rate [32]. Information on former smokers was not collected. Another limitation is the small sample size, so multicenter studies are needed. One limitation may be the lack of detailed information on the treatment, but there is no scientific evidence or large multicenter trials that show that cardiovascular drugs can significantly prevent occurrence of coronary calcification or significantly limit progression or reduce calcium score [33, 34].

CONCLUSIONS

Our findings suggest that the geometric features of LM trifurcation are related to the risk of atherosclerosis. Wider LM trifurcation angulation is closely correlated with LCA disease and earlier calcified plaque onset. Measurement of the LM trifurcation angle may be used to identify patients at higher risk of coronary artery disease. The prognostic value of our observations warrants further research and observational studies.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

Conflict of interest: None declared.

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Hemodynamic profile changes in reaction to nitroglycerin in patients with heart failure with mildly reduced ejection fraction: A pilot study

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INTRODUCTION

There are 3 types of heart failure (HF) — with reduced (HFrEF; ≤40%), mildly reduced (HFmrEF; 41%–49%), and preserved (HFpEF; ≥50%) left ventricular ejection fraction (LVEF) [1]. The HFmrEF type is the least known. Like the HFrEF group, the HFmrEF type is characterized by a higher prevalence of younger, male individuals with a history of coronary artery disease. On the other hand, ambulatory HFmrEF patients have lower mortality (more like HFpEF).

This study aimed to assess the hemodynamic profile of patients with HFmrEF at rest and after sublingual administration of 0.4 mg of nitroglycerin (NTG) in comparison to those with HFrEF and HFpEF using noninvasive electrical cardiometry (EC).

EC is based on thoracic bio-impedance changes during the cardiac cycle [2]. Notwithstanding its limitations, EC is a useful tool in the management of patients with HF [3, 4]. Vein and artery dilatation after NTG administration leads to preload and afterload reduction and consequently to a stroke volume (SV) and cardiac output (CO) increase [5].

METHODS

The study was performed in clinically stable subjects (with a history of HF as well as HF diagnosed *de novo)* on the last day of hospitalization for acute decompensated heart failure (ADHF), defined as an exacerbation of typical HF signs/symptoms, requiring the administration of iv. diuretics (at least 40 mg of furosemide or its equivalent). The control groups for HFmrEF patients were those with HFpEF and HFrEF. There was no control group of healthy subjects. The clinical profile of patients was assessed by the data from medical interviews and records, laboratory test results, and measured echocardiographic parameters while the noninvasive hemodynamic profile, at rest and after the NTG administration, was assessed by EC using the ICON® (OSYPKA Medical) device. The most important exclusion criteria were age <18 years; ADHF caused by: acute coronary syndrome, significant valvular disease, tachyarrhythmia; percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) during the current hospitalization; severe dyspnea or orthopnea; chronic lung diseases; stage 5 chronic kidney disease or on dialysis; contraindications for NTG administration (including BP <90/60 mm Hg); implantable cardiac devices with a "rate response" mode (contraindication for EC); the ICON® report quality index below 90% (to avoid potential bias in readings obtained from patients with atrial fibrillation or overweight).

After approximately 60 cardiac cycles (stable readings on the device), the first EC report was generated (at rest) and the second — 2–3 minutes after NTG administration. Each report (automatically generated by the ICON®) contains the mean values (from the last 60 heart cycles) of each measured hemodynamic parameter. A control blood pressure measurement was performed only in the case of a reported adverse event.

The χ^2, χ^2 with Yates' correction, and Fisher's exact tests were carried out to compare categorical variables, depending on the number of counts. The difference in continuous variables was calculated with the Mann-Whitney U test (when 2 groups were compared) or the Kruskal-Wallis test (in the case of >2 groups). The

majority of variables did not follow normal distributions (as verified with the Shapiro-Wilk test). Therefore, all numerical variables are presented as median and interquartile range, and nonparametric tests were used for all calculations (as they presented a comparable statistical power to their parametric equivalents in the case of the normally distributed variables).

The study was approved by the Ethics Committee at the Medical University of Łódz (RNN/108/19/KE).

RESULTS AND DISCUSSION

Overall, 45 patients (hospitalized between January 1 and June 30, 2021), were enrolled in this pilot study, including 15 consecutive patients from each HF type, and most of them were men (n = 32; 71%). The full clinical study group characteristics and their hemodynamic profile changes are presented in Supplementary material, *Tables S1* and *S2*. Diabetes was significantly more frequent in the HFpEF group. The HFrEF group had a higher left ventricular end-diastolic dimension (P <0.001) and lower right ventricular systolic function (tricuspid annular plane systolic excursion [TAPSE]; P = 0.003). All patients were receiving β-blockers (except for nebivolol or carvedilol), mineralocorticoid receptor antagonists, angiotensin-converting-enzyme inhibitors (ACEI; 86.7%) or angiotensin II receptor antagonists (ARB, 13.3%), and loop diuretics (only furosemide or torsemide). The study was completed before the latest HF guidelines release and none of the patients was receiving angiotensin receptor-neprilysin inhibitor (ARNI) or sodium-glucose co-transporter-2 inhibitors (SGLT2i).

The results of the hemodynamic profile at rest showed a lower systolic time ratio (STR; P = 0.02) and pre-ejection period (PEP; P = 0.049) in the HFmrEF group in comparison to the HFrEF group.

After NTG administration, in patients with HFmrEF, in comparison to HFrEF, we observed a decline in the median of stroke volume and stroke volume index (SV/SI; P = 0.01/0.02), cardiac output and cardiac index (CO/CI; P = 0.01/0.01), cardiac performance index (CPI; P = 0.049), and corrected flow time (FTC; P = 0.04), and an increase in systemic vascular resistance and its indexed values (SVR/SVRI; P = 0.03/0.03).

The median of change in the following parameters: SV, SI, CO, CI, FTC, SVR, SVRI, and CPI after NTG administration in the HFmrEF group had an opposite direction in comparison to the patients with HFrEF (P <0.05) (Figure 1, Supplementary material, *Table S2*). This effect was observed in some patients in all study groups, however, most frequently in the HFmrEF group (number of patients with the opposite NTG reaction – HFrEF, n = 2; HFpEF, n = 3; HFmrEF, n = 6) — all three groups were compared with Fisher's exact test (performed on a 3×2 table), and no difference was observed (P = 0.19). Unfortunately, none of the analyzed clinical parameters showed an association with a particular type of NTG reaction (Supplementary material, *Table S1*).

To the best of our knowledge, this is the first study to evaluate hemodynamic profile changes in HFmrEF patients in comparison to those with HFpEF and HFrEF.

Our study confirms the intermediate character of HFmrEF patients' clinical profile, which is widely described in the literature [6–9]. The hemodynamic profile of all three groups shared the same characteristics at rest with significant differences exclusively in STR and PEP between HFmrEF and HFrEF patients. Unfortunately, there is no data in the current literature referring to this observation, especially SVR which can be measured only by the ICON® device.

The analysis of the hemodynamic profile after NTG administration brings the most intriguing results. Firstly, we found significant differences between HFmrEF and HFrEF in 8 parameters, including the main hemodynamic parameters associated with blood flow: SV/SI, CO/CI, and SVR/SVRI. Moreover, the median change in the same parameters in the HFmrEF group (SV, SI, CO, CI, FTC, SVR, SVRI, and CPI) had an opposite direction. In the case of the HFpEF and HFrEF patients CO and SV were increasing, while they were decreasing in HFmrEF. In the case of SVR/SVRI, the decline in the HFrEF and HFpEF patients was accompanied by an icrease in those with HFmrEF. The opposite reaction to NTG (CO and SV decline and SVR increase) was observed in some patients in all study groups; however, most frequently in the HFmrEF group, and a higher incidence of this phenomenon caused the opposite direction of the median change of each parameter.

In the randomized clinical trial with NO-donor — BMS-986231 (HFrEF patients only), the authors observed a slight but statistically significant decline in SV and SVI [10]. In one study, the invasive SV and CO measurements in 257 patients with HF showed that HFrEF patients had a greater increase in SV and CO in comparison to HFpEF [11], caused by more frequent opposite NTG reaction in HFpEF (HFpEF: 35% vs HFrEF: 9%; P <0.0001). The reaction was caused by the increased end-diastolic pressure of left ventricle (LV) (preload). Again, patients with HFmrEF were not included, as a mean (SD) EF was 22% (9%) and 63% (6%) (P <0.0001), so the frequency of the opposite NTG reaction in HFmrEF remains unknown. Our study suggests that the incidence of this phenomenon is the highest in the HFmrEF group and may be caused by the combination of both systolic and diastolic dysfunction of LV (confirmed in all HFmrEF subjects by echocardiography).

The most important limitation of the study is a small group of patients and lack of a control group of healthy subjects. Further studies on a greater population are required to confirm our observations.

In conclusion, HFmrEF differs significantly from HFrEF in terms of changes of the hemodynamic profile after NTG administration, considering EC parameters of the blood flow (SV, SI, CO, CI, SVR, SVRI) and heart muscle contractility (CPI, FTC). The median change of all the above-mentioned parameters showed the opposite direction after NTG

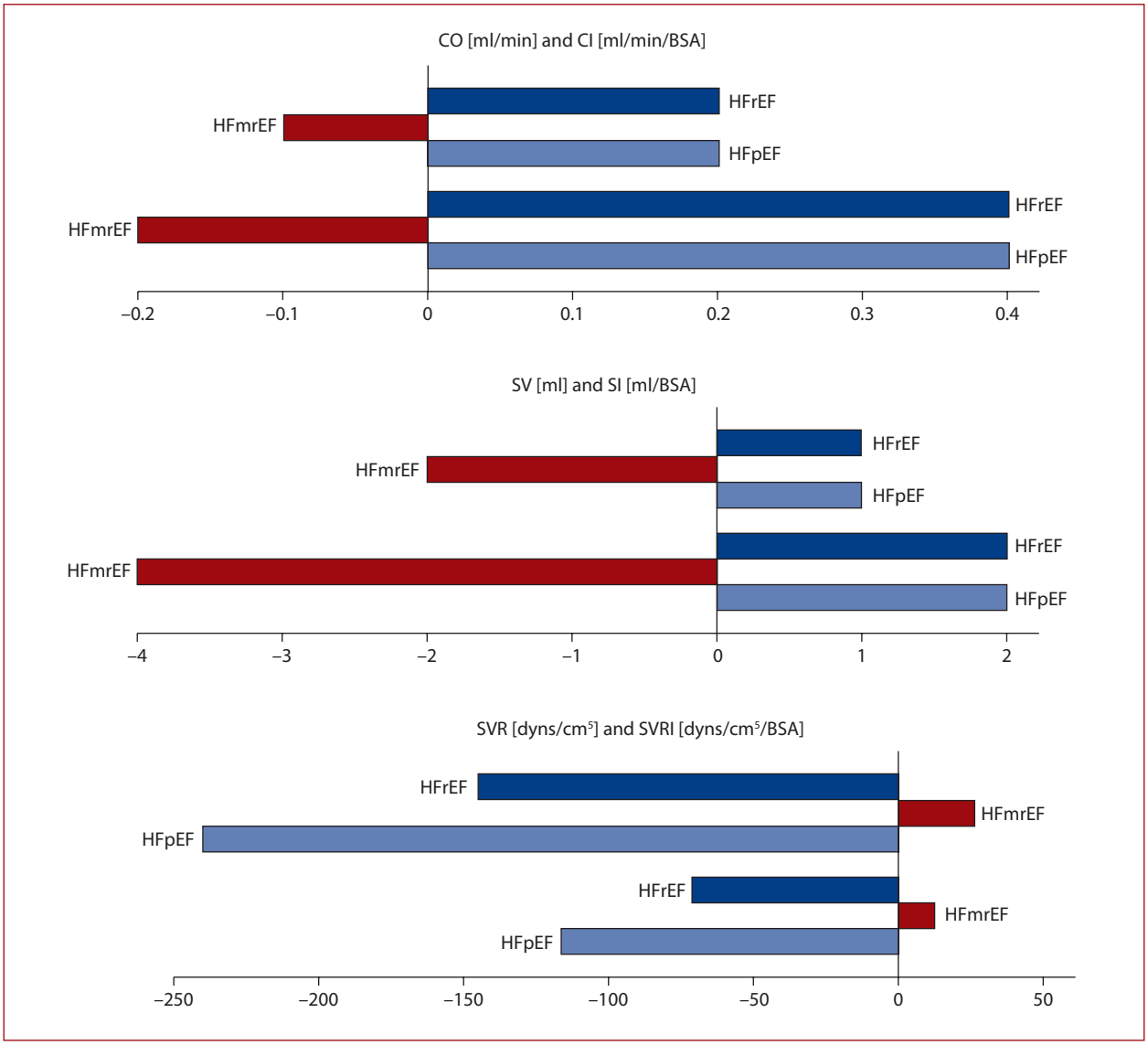

Figure 1. Median change in basic hemodynamic parameters after nitroglycerin administration (HFmrEF vs. HFpEF: *P* = NS; HFmrEF vs. HFrEF; *P* <0.05)

Abbreviations: BSA, body surface area; CI, cardiac index; CO, cardiac output; dyn, force unit in the CGS metric system; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; SI, stroke volume index; SV, stroke volume; SVR, systemic vascular resistance; SVRI, systemic vascular resistance index

administration in the HFmrEF group in comparison to the HFpEF and HFrEF groups. The opposite reaction to NTG occurred most frequently in the HFmrEF group.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

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Role of global longitudinal strain in evaluating radiotherapy--induced early cardiotoxicity in breast cancer: A meta-analysis

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INTRODUCTION

The incidence of breast cancer ranks first among all female malignant tumors [1]. Radiotherapy (RT) plays an important role in the management of breast cancer, reducing the risk of local relapse and specific death. However, RT can increase the risk of cardiovascular morbidity and mortality due to incidental radiation of cardiac structures [2]. The reduction of left ventricular ejection fraction (LVEF) mainly leads to significant left ventricular dysfunction. It is noteworthy that myocardial function can change greatly without any decline in LVEF [3].

Global longitudinal strain (GLS) assessed by speckle-tracking echocardiography (STE) is a new technique for detecting and quantifying subtle disturbances in left ventricular systolic function [4]. In this meta-analysis, we aimed to investigate the role of GLS in evaluating radiotherapy-induced early cardiotoxicity in breast cancer.

METHODS

The present study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis. Two researchers independently conducted a literature search through PubMed, EMBASE, Web of Science, Cochrane Library, WanFang, and CNKI databases in January 2010 and March 2022, and the language was limited to Chinese or English. The search words mainly included "breast cancer", "radiotherapy", "cardiotoxicity", echocardiography", etc.

Inclusion and exclusion criteria

Our inclusion criteria were: (1) breast cancer patients who received adjuvant RT with or without adjuvant chemotherapy; (2) speckle-tracking echocardiography performed before radiotherapy and during follow-up and obtained the result of LVEF and GLS. The exclusion criteria were: (1) left and right breast cancer data were not recorded separately; (2) studies were duplicated or data overlapped; (3) letters, case reports, editorials, or reviews.

Data extraction

Two investigators independently extracted the following data: study characteristics (authors, year of publication), participant characteristics (age, sample size of different groups, the proportion of patients undergoing chemotherapy and targeted therapy, radiotherapy dose, use of cardioprotective agents).

Statistics analysis

Data were entered into RevMan 5.4 software to conduct the meta-analysis and heterogeneity analysis. Since the change in LVEF and GLS from baseline to post-RT was regarded as continuous data, the weighted mean difference (WMD) and 95% confidence intervals (95% CI) were used to draw a forest plot. A two-sided P-value <0.05 was considered statistically significant in the WMD analysis. Cochran's Q test and I^2 statistics were conducted to assess the heterogeneity of the effects. If P-values >0.1 or I^2 statistics <50% were observed, it can be considered that there was no obvious

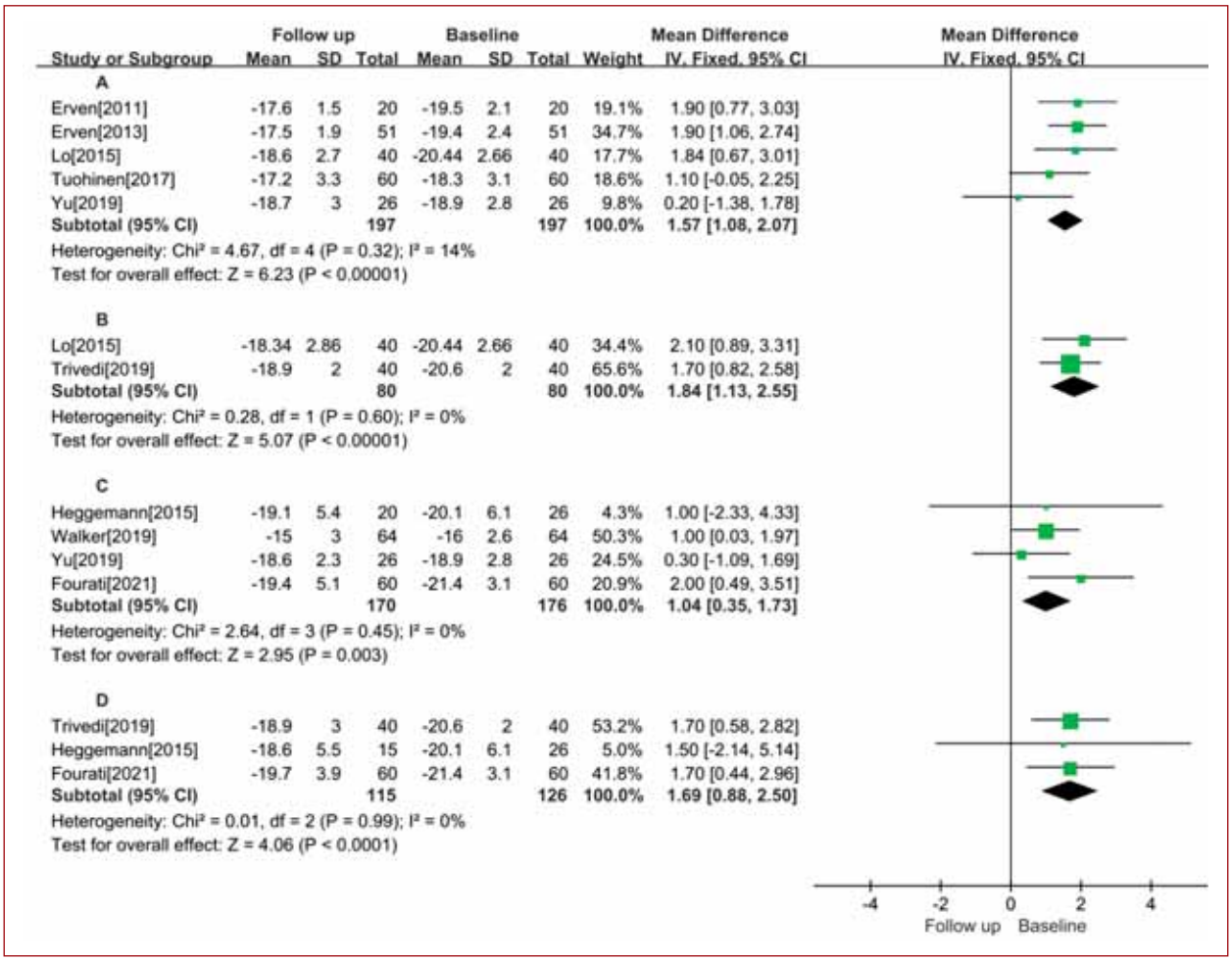

Figure 1. A. GLS changes in left-breast cancer before and after radiotherapy. **B.** GLS changes in left-breast cancer at 6 weeks after radiotherapy. **C.** GLS changes in left-breast cancer at 6 months after radiotherapy. **D.** GLS changes in left-breast cancer at 12 months after radiotherapy
Abbreviation: GLS, global longitudinal strain

heterogeneity between studies, and a fixed effects model was used to pool data. If heterogeneity was detected, we conducted subgroup analysis to explore the source of heterogeneity.

RESULTS AND DISCUSSION

Finally, 9 articles [3, 5–12] were included in the meta-analysis. The literature retrieval process is shown in Supplementary material, *Figure S1*, and the basic information of the included literature is shown in Supplementary material, *Table S1*.

The average LVEF ranged between 60.9% to 73.3% before radiotherapy and 58.7% to 70.5% after radiotherapy. Merging analysis showed that LVEF after radiotherapy was lower than baseline (–0.98 WMD; 95% CI, –1.88 to –0.08; $P = 0.03$), and there was no heterogeneity among studies ($I^2 = 13\%$, $P = 0.33$, Supplementary material, *Figure S2A*). At 6 months of follow-up, the results of LVEF did not change (–0.83 WMD; 95% CI –3.09 to 1.43; $P = 0.47$), with no heterogeneity among studies ($I^2 = 0\%$, $P = 0.84$, Supplementary material, *Figure S2B*). As for the right breast cancer, LVEF after radiotherapy was not different (–0.17 WMD; 95% CI –2.07 to 1.72, $P = 0.86$), and there was no heterogeneity among studies ($I^2 = 0\%$, $P = 0.54$, Supplementary material, *Figure S3*).

After radiotherapy for left breast cancer, GLS decreased, with average GLS values in the range of –21.4% to –16.0% before radiotherapy and –18.7% to –17.2% after radiotherapy (1.57 WMD; 95% CI, 1.08–2.07; $P < 0.001$). There was no significant heterogeneity among studies ($I^2 = 14\%$; $P = 0.32$, Figure 1A). GLS was lower than baseline at 6 weeks, 6 months, and 12 months after radiotherapy (1.84 WMD; 95% CI, 1.13–2.55; $P < 0.001$, Figure 1B), (1.04 WMD; 95% CI, 0.35–1.73; $P < 0.003$, Figure 1C), (1.69 WMD; 95% CI, 0.88–2.50; $P < 0.001$, Figure 1D), with no heterogeneity among studies. After radiotherapy for right breast cancer, the result of GLS was 0.18 WMD; 95% CI, –0.55 to 0.91; $P = 0.62$, and there was no heterogeneity among studies ($I^2 = 0\%$, $P = 0.58$, Supplementary material, *Figure S4*).

This meta-analysis showed that LVEF of patients with left breast cancer decreased slightly after radiotherapy but remained within the normal range, while LVEF of patients with right breast cancer did not change significantly after radiotherapy. Erven et al. [3] found that baseline LVEF was

lower in patients receiving chemotherapy compared to the patients not receiving chemotherapy. However, LVEF reduction caused by radiotherapy was the same, so it did not affect the results of this meta-analysis.

The results also showed that GLS decreased significantly at 6 and 12 months after radiotherapy. Heggemann et al. [12] demonstrated that GLS was still lower than baseline at 24 months after radiotherapy but better than 6 months after radiotherapy. Except for GLS, global myocardial deformation indices also include global radial (GRS) and circumferential strain (GCS). Stokke [13] showed that GLS was the first marker to be affected in many physiological and pathological processes, possibly because most of the longitudinal fibers were located in the subendocardium which was most vulnerable to damage. Perhaps it is not enough to focus on global change. Walker [4] focused on regional myocardial function and suggested that the longitudinal strain change may be more relevant in the endocardial layer, in particular, in the most exposed areas of the left ventricle, corresponding to the apical region and the left anterior descending artery (LAD) territory. In a study by Tuohinen et al. [7], patients with left-sided breast cancer experienced apical and global decline, whereas patients with right-sided breast cancer showed basal changes with no changes in GLS. In the future, we need to conduct more studies to confirm these observations. After all, early recognition of radiation-induced heart disease and early use of cardioprotective agents were critical to improving the quality of life of breast cancer survivors [14, 15].

Limitations of this meta-analysis include (1) the time of assessment during radiotherapy and follow-up was inconsistent, which may have some influence on the detection of myocardial changes; (2) differences in delineation method and dose limitation of cardiac targets in various centers also lead to differences in myocardial changes; (3) the research came from various centers, and different instruments were used for STE detection; (4) the follow-up time was inconsistent; (5) only two studies considered the impact of cardioprotective agents.

In conclusion, GLS is a good parameter to identify early radiation-induced heart disease in left-side breast cancer. As for right-side breast cancer, the segmental changes may be more important.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska.

Article information

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Use of orbital atherectomy in coronary artery disease with severe calcification: A preliminary study

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INTRODUCTION

Severe coronary artery calcifications occur in about 10% of patients undergoing percutaneous coronary intervention (PCI). They constitute a strong independent predictor of adverse cardiovascular events [1]. Even though the risk factors and pathomechanisms leading to severe coronary calcification are well understood, options for effective treatment remain insufficient [2, 3].

In the presence of severe calcification, standard PCI has inferior immediate and long-term outcomes [4–6]. In this situation, advanced lesion modification techniques are indispensable to improve PCI outcomes. Dedicated balloons and ablative techniques are available. Rotational atherectomy (RA) is the oldest and best-recognized ablative technique [7–9]. It is generally acknowledged that superficial modification of calcified atherosclerotic lesions is the optimal mechanism of action in RA. Orbital atherectomy (OA) is the second ablative technique that applies the same procedural approach, albeit using a different device. OA was first introduced into clinical practice about 10 years ago in the US. Currently, in the US the number of interventions using OA and RA is comparable [10, 11]. For a few years, OA has been implemented in Europe; the first procedure in Poland was performed in December 2021. The potential advantages of OA over RA include the ability to ablate calcifications both when the device is moved forward (anterograde) and backward (retrograde) (thus eliminating the risk of coronal entrapment within the lesion), lesser impact on circulatory hemodynamics (no drop in pressure during ablation, particularly beneficial in the case of hemodynamically unstable patients), more efficient ablation of calcifications, and lesser risk of microvascular obstruction during and after the procedure. On the other hand, some data indicate a higher rate of dissections and perforations with OA [12]. In the present study, we present data on first interventions with OA with the aim of showing the immediate safety and efficacy of the procedure.

MATERIALS

The study included 25 consecutive patients who underwent coronary interventions with OA at referral cardiology centers in Białystok, Kraków, and Zabrze between December 2021 and June 2022. The primary inclusion criterion was the presence of *de novo* stenosis ≥80% with severe calcification in a vessel of 2.5–4.0-mm diameter on angiography.

All the interventions were performed as elective procedures with OA as a primary approach. All stages of interventional treatment, including antiplatelet and perioperative therapy, were standard and remained in concordance with guidelines. Intravascular imaging was broadly recommended before the intervention and to assess the procedure's outcomes. A 1.25-mm ablative device (crown) was used at two standard speeds of 80 000 and 120 000 rpm, depending on the arterial anatomy and calcification pattern.

Higher speed and slower coronal movement within the artery allowed for a greater degree of calcific modification. In OA, effective action is possible while pushing on the stenosis and withdrawing the device through the stenosis. Movement along the vessel was performed in a uniform motion at the recommended speed of about 1–3 mm/s.

After ablation, non-compliant balloon inflation was a routine, scoring/cutting balloons, if necessary, were followed by implantation of the drug-eluting stents. Procedural success was defined as completing lesion modification with OA with subsequent stent placement. Evaluation of the intervention (occurrence of major adverse cardiovascular events) was performed in the perioperative period.

RESULTS AND DISCUSSION

The basic characteristics of patients and treatment data are shown in Table 1.

All patients qualified for OA had complex atherosclerotic coronary lesions, and the median SYNTAX Score was 28 (23–33). The presence of severe calcifications was demonstrated in all patients on coronary angiography and/or intracoronary imaging. In line with the current guidelines, in such cases the application of modification methods (RA, OA, or lithotripsy) is advised [13]. Radial access was used in 24 patients (96%); it allowed for minimizing the risk of vascular complications, reducing hospitalization time, and maintaining comparable procedural efficacy as in femoral access. There was a 100% success rate of OA. All patients received DES optimally implanted, with an average length of 49 (30–66) mm, and full TIMI3 (Thrombolytics in Myocardial Infarction) flow in 24 patients (96%).

In comparison with more widely used RA, OA seems to have a couple of differences. In the authors' subjective opinion, compared to RotaWire, the OA ViperWire Advance® guidewire allows for superior deliverability and maneuverability. In most cases, the guidewire can be delivered directly without a microcatheter and as a result of its larger diameter, subsequent steps of intervention can be done easily with a single guidewire. Presumably, OA can modify the calcified plaque to a greater extent by creating longer and deeper incisions. Finally, the plaque microparticles generated during OA are smaller than in RA (2 μm vs. 5 μm) [14]. Assuming their easier elimination from the microcirculation, this may translate into a lower frequency of coronary flow disturbances. Currently, no data support the above differences as clinically significant [15]. In our study, only one patient showed transient flow impairment, and the criteria for the diagnosis of IVa infarction were met in the postoperative period. It was the PCI with OA in the dominant right coronary artery with retrograde circulation to the left coronary artery, in a patient with a history of CABG with nonfunctioning venous bypasses. Fortunately, the patient was discharged in good condition after several additional days of hospitalization. Additionally, in two patients temporary conduction disturbances not necessitating electrostimulation were observed, in another two

Table 1. Characteristics of the study participants

Baseline characteristics (n = 25)	
Age, years, median (IQR)	71 (68.5–72.5)
Male sex, n (%)	23 (92)
EuroSCORE II, median (IQR)	2.4 (1.5–4)
BMI, kg/m^2, median (IQR)	27.8 (27–32.3)
LVEF, %, median (IQR)	54 (43–60)
Previous PCI, n (%)	17 (68)
Previous CABG, n (%)	9 (36)
Previous ACS, n (%)	8 (32)
Previous stroke, n (%)	3 (12)
Atrial fibrillation, n (%)	10 (40)
Diabetes mellitus, n (%)	10 (40)
Chronic kidney disease, n (%)	6 (24)
Peripheral artery disease, n (%)	8 (32)
Angiographic details	
SYNTAX I, median (IQR)	28 (23–33)
SYTNAX II CABG, median (IQR)	31 (28.5–44)/35.9 (28.8–50.8)
SYTNAX II PCI, median (IQR)	
Single vessel CCS, n (%)	3 (12)
Multivessel CCS, n (%)	14 (56)
Chronic total occlusion, n (%)	(3) 12
Procedural details	
Procedural success, n (%)	25 (100)
Radial access, n (%)	24 (95)
Treated artery	
Left main, n (%)	6 (24)
Left anterior descending artery, n (%)	12 (48)
Circumflex artery, n (%)	3 (12)
Right coronary artery, n (%)	4 (16)
PCI in CTO, n (%)	3 (12)
PCI in bifurcation, n (%)	4 (16)
IVUS, n (%)	21 (84)
OCT, n (%)	4 (16)
Scoring balloon, n (%)	2 (8)
Cutting balloon, n (%)	1 (4)
Length of all stents, mm, median (IQR)	49 (30–66)
Average diameter of all stents, mm, median (IQR)	3.5 (3–3.5)
Total procedure time, min, median (IQR)	90 (80–105)
Total fluoroscopy time, min, median (IQR)	25.6 (18.7–32)
K, mGy, median (IQR)	1029 (679–1538)
Contrast volume, ml, median (IQR)	170 (150–230)
TIMI 3 score post-procedure, n (%)	24 (96)
Acetylsalicylic acid prescribed at discharge, n (%)	25 (100)
Clopidogrel prescribed at discharge, n (%)	25 (100)
Postprocedural complications	
Slow flow, n (%)	2 (8)
No flow, n (%)	0 (0)
Coronary perforation, n (%)	0 (0)
Tamponade, n (%)	0 (0)
Atrioventricular block, n (%)	2 (8)
Acute kidney injury, n (%)	0 (0)
Vascular complications of PCI, n (%)	2 (8)
IVa myocardial infarction, n (%)	1 (4)
In hospital MACE, n (%)	1 (4)

Chronic kidney disease was defined as the presence of kidney damage or an estimated glomerular filtration rate (eGFR) less than 60 ml/min/1.73 m^2, persisting for three months or more, irrespective of the cause

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; CTO, chronic total occlusion; IQR, interquartile range; IVUS, intravascular ultrasound; K, kinetic energy released per mass unit; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular events; Me; median; OCT, optical coherence tomography; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction grade flow

cases, minor forearm hematomas occurred not requiring surgical intervention.

A selection of a strategy and evaluation of the treatment for patients with severe coronary artery calcification is challenging. The clinical characteristics of patients and the complexity of atherosclerotic lesions undergoing PCI clearly predefine high cardiovascular risk. In addition, advanced and elaborated PCI techniques increase the risk of adverse events in the perioperative period. In this report, the prevalence of adverse events was low and comparable to the data from large registries [10, 11]. It should be emphasized that most complications during OA or RA procedures are the direct consequence of patients' high clinical burden and the complexity of the lesions treated. In such difficult cases, ablative methods very often are the sole treatment option. They are used not to generate complications but to overcome them and ensure optimal and effective treatment of patients. Currently, the ECLIPSE trial is recruiting patients to evaluate treatment strategies for severe coronary artery calcification by randomizing patients to OA or conventional angioplasty with implantation of DES stents [15]. The results of this trial will certainly provide important information for the application of OA.

In conclusion, in the analyzed group of patients, the OA procedure turned out to be effective and safe for modifying massively calcified coronary artery lesions. This procedure has a low and acceptable rate of adverse events. Further study in a large group of patients is needed to fully evaluate the procedure and to define indications for its use. At present, the indications for OA overlap with those of the more widely used RA.

Article information

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Transcatheter aortic valve replacement in a patient with severe aortic regurgitation following left ventricular assist device implantation

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Left ventricular assist devices (LVAD) are used as a bridge to heart transplant or "destination" therapy in patients with end-stage congestive heart failure (HF) [1]. However, LVAD support may induce hemodynamic and structural variations in the aortic root that may result in aortic regurgitation (AR) in even 30% of patients [2]. Severe AR in patients with LVAD leads to decompensated HF due to the constant loop of flow between the ascending aorta and the LVAD, resulting in poor cardiac output despite apparent normal device function.

A 55-year-old female was admitted due to cardiac decompensation — class IV of the New York Heart Association (NYHA) Functional Classification. At admission, she presented with hypotension, massive leg edema, and ascites despite optimal medical treatment. An electrocardiogram showed sinus rhythm of 80 bpm and left bundle branch block. On transthoracic echocardiogram (TTE), the systolic function of the left ventricle was severely reduced with ejection fraction (LVEF) of 15%, and, additionally, severe AR was found (Figure 1A). The patient had undergone implantation of an implantable cardioverter defibrillator (ICD) and LVAD (HeartWare, Medtronic, Dublin, Ireland) 3 years before admission. The level of NT-proBNP was elevated up to 8149 pg/ml. The initial treatment was focused on intravenous diuretic therapy, fluid intake reduction, and vasoconstrictors (noradrenaline, dobutamine, and milrinone) infusion. Nonetheless, AR remained still severe despite

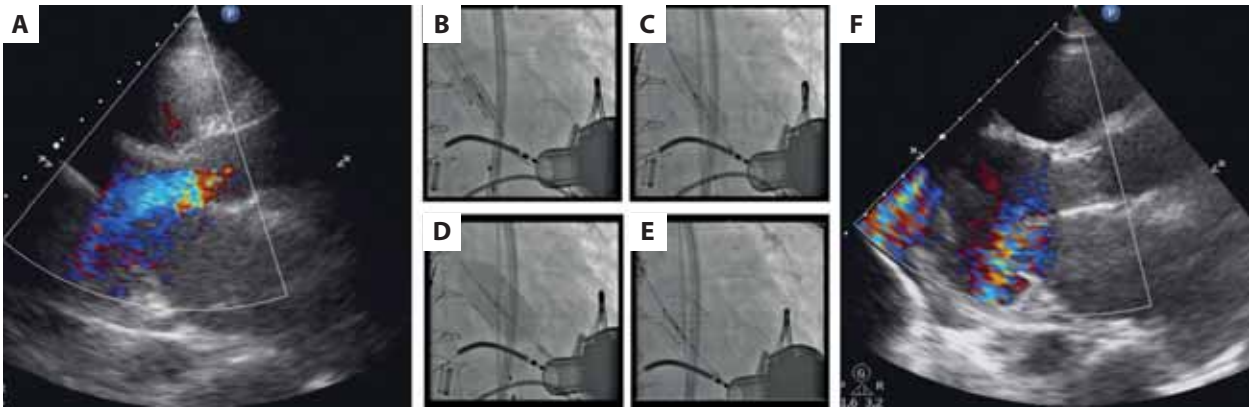

Figure 1. A. Severe aortic regurgitation imaged by transthoracic echocardiography. **B–E.** Transcatheter aortic valve implantation in fluoroscopy showing the balloon-expandable prosthesis (Edwards S3 23 mm plus 1.5 cm^3) positioning and deployment. **F.** Postprocedural transthoracic echocardiography assessment showing no AR and the optimal transcatheter heart valve position

treatment, so the case was discussed with the Heart Team and the patient was scheduled for urgent transcatheter aortic valve implantation (TAVI). A computed tomography scan showed favorable anatomy in terms of the non-calcified aortic valve and peripheral access. The TAVI procedure was performed in analgosedation using femoral access and TTE guidance. A 23-mm Edwards Sapien S3 valve (Edwards Lifesciences, Irvine, CA, US) was advanced over an Amplatz Ultra-Stiff wire (Cook Medical, Bloomington, IN, US) and positioned within the aortic annulus (Figure 1B–E). Aortic root injections were performed. With rapid pacing, the valve was deployed with repeated aortic root injections. The valve was observed in this position for ca. 5 minutes to check for its eventual migration into the left ventricle. Just before valve implantation, the LVAD flow rate was slowed. Over ca. 5 minutes, the LVAD flow rate was ramped up to baseline rotations with continuous observation under echocardiography and cine angiography. The procedure was uneventful, the implanted valve was stable with no perivalvular regurgitation and no coronary obstruction (Figure 1F). The patient was discharged with NYHA II symptoms, and LVEF remained unchanged. After six months, the patient presented with NYHA II symptoms, and no major cardiovascular events occurred.

Patients with LVADs and severe AR are high-risk candidates for surgical aortic valve replacement due to end-stage HF and frequent medical comorbidities. TAVI can be considered in these patients as a less risky intervention leading to an immediate and significant improvement in cardiac hemodynamics. However, it is important to recognize the anatomic challenges due to inadequate calcification for anchoring the prosthesis. Annular dilation and high flow rates in the ascending aorta from the LVAD outflow cannula [3] significantly increase the risk of inadequate sealing, valve embolization, and significant residual PVL.

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Radial artery pseudo-aneurysm detected with a portable handheld ultrasound device in a COVID-19 patient

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A 78-year-old male patient with COVID-19 was admitted to the emergency room for hemorrhagic shock related to a ruptured middle-colic artery aneurysm. In the days before admission, he was treated for a COVID-19 infection with monoclonal antibodies. In the emergency room, he appeared in a very serious clinical condition, was intubated and treated with inotropic drugs. Embolization of the middle colic artery was performed to stop active bleeding, and cannulation of the left radial artery was performed.

At admission to the medical ward, a pseudoaneurysm of the radial artery (Figure 1A) was detected with a portable ultrasound device (Butterfly IQ+). In the following days, the size of the pseudoaneurysm increased (Figure 1B).

The pseudo-aneurysmal formation was later confirmed by computed tomography (CT) (Figure 1C). CT showed a diameter of about 8 mm at the level of the distal third of the radial artery, corresponding to the distal radial epiphysis. The following day a sudden rupture of the pseudoaneurysm was observed. Selective arteriography of the radial artery confirmed the pseudoaneurysm of the distal third of the artery with active spread of contrast medium. The pseudoaneurysm was embolized with a microcatheter. No blood flow was detected after embolization with a portable ultrasound device (Figure 1D). The patient was discharged in good clinical condition.

Pseudoaneurysm of the artery represents a rare complication (incidence of 0.048% [1]) that can occur after attempts to canalize the radial arteries [2]. We cannot exclude that COVID-19 increased the risk of fragility of the arterial wall. Inflammation of the arteries and increased oxidative stress could play a pivotal role in increasing vascular complications in COVID-19 patients [3, 4]. Some studies reported rupture of aneurysms or dissections aggravated by COVID-19 [5].

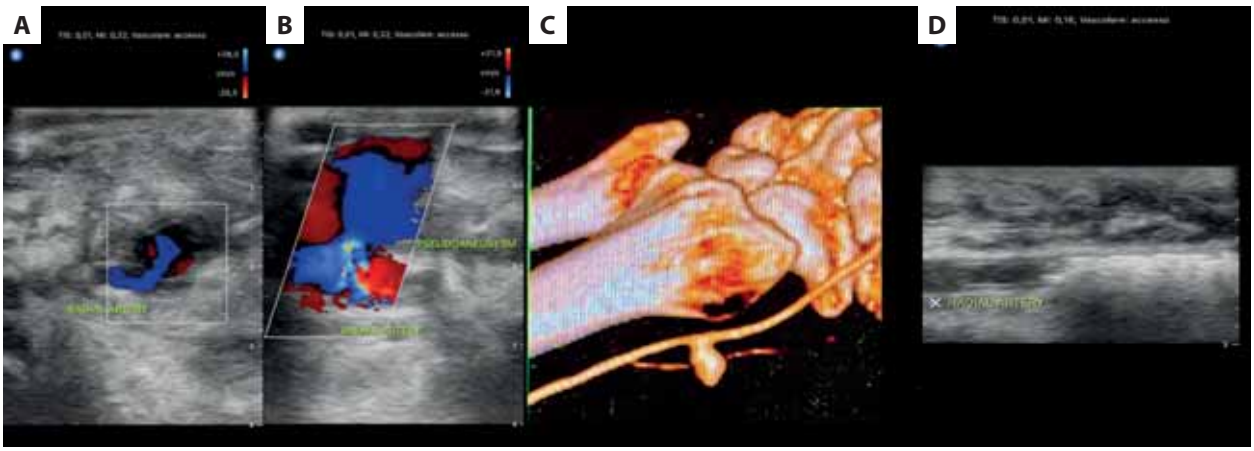

Figure 1. **A.** Pseudoaneurysm of the radial artery detected with a portable ultrasound device (Butterfly IQ+) upon admission to the medical ward. **B.** Increased size of pseudoaneurysm evaluated with a portable ultrasound device. **C.** Pseudoaneurysm evaluated by computed tomography. **D.** No blood flow after embolization evaluated with a portable ultrasound device

Portable ultrasound reliably diagnoses radial artery pseudoaneurysms and is a valuable tool for early detection of vascular diseases.

Article information

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When an interventional cardiologist needs to be a vascular surgeon: Successful management of coronary stent loss in a nonagenarian

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Stent loss and embolization have not been entirely eradicated even though they have become rare (<1%) since factory crimping was introduced. Stent retrieval techniques are often challenging, and evidence for their effectiveness is restricted mainly to case reports and case series [1]. Here, we present a case of a 91-year-old male who was admitted to the cath lab due to chest pain, complete atrioventricular block, and electrocardiography (ECG) recording revealing ST-segment elevation myocardial infarction of the inferior wall. The patient had a history of permanent atrial fibrillation, dyslipidemia, gout, and two episodes of stroke. The immediate coronary angiography showed lesions not exceeding 50% in diameter, stenosis in the left coronary artery, and 90% stenosis in the proximal segment with complete occlusion in the mid-portion of the right coronary artery (RCA) (Figure 1A). Initially, the successful predilatation was performed in the proximal and mid-RCA segments with a 3.0 × 20 mm balloon catheter. During stent advancement (Alex Plus 4.5 × 22 mm, Balton, Poland) to the mid/distal RCA segment (Figure 1B, Supplementary material, *Video S1*), the

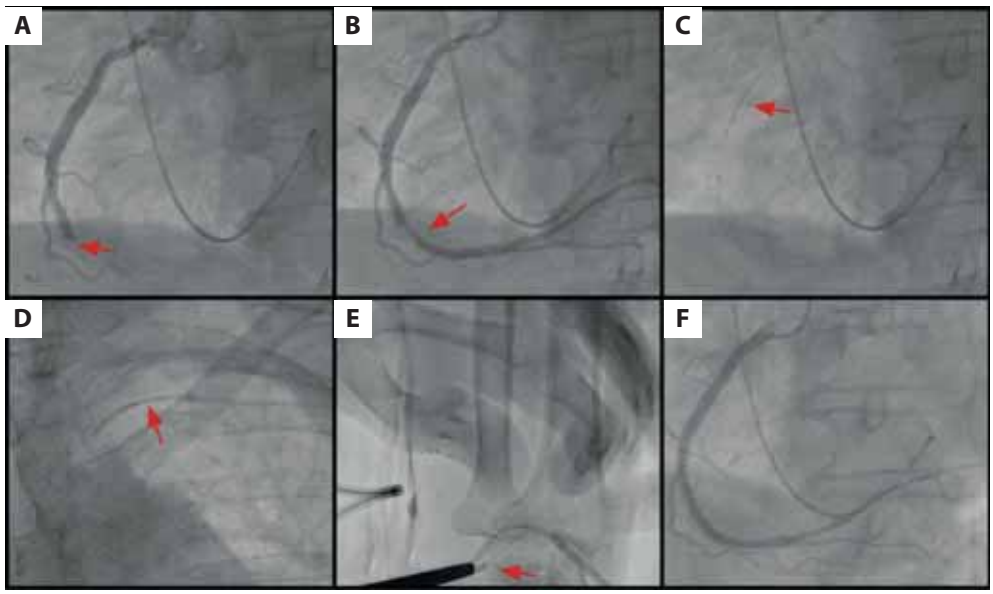

Figure 1. A. Baseline view of the right coronary artery (RCA) (arrow). **B.** The lesion in the mid/distal RCA segment remained after predilatation (arrow). **C.** Stent lost in the proximal/mid RCA with the balloon catheter in front of it (arrow). **D.** Removal of the stent and inflated balloon through the left subclavian artery (arrow). **E.** Removal of the stent with the vascular pean through the incision in the left radial artery (arrow). **F.** The final view of the procedures with two stents deployed in the RCA

stent detached from the balloon catheter and remained in the proximal/mid RCA (Figure 1C). The coronary balloon catheter River 1.5 × 15 mm (Balton, Poland) was advanced throughout the stent, then it was inflated at 4 atm, and the whole system was retrieved from the RCA (Figure 1D, Supplementary material, *Video S2*). However, we could not introduce this system into the vascular sheath. After some struggle, we decided to cut the skin around the access site in the left radial artery, and we successfully removed the stent with a clamp pean (Figure 1E, Supplementary material, *Video S3*). The incision was closed with two non-absorbable sutures, and the procedure was continued from the right radial artery. Before stent advancement, the lesions were predilated with 3.5 × 20 mm and 4.0 × 20 mm balloon catheters (River). Finally, the 4.0 × 22 mm Alex Plus stent was deployed distally and postdilated with a non-compliant balloon catheter River NC 4.5 × 20 mm at 18 atm (Balton). In the proximal segment, we implanted a 4.5 × 22 mm Alex Plus stent (18 atm) (Figure 1F). We restored the coronary lumen and coronary flow completely (TIMI3), and the patient was discharged after three days without permanent cardiac stimulation on clopidogrel (75 mg/d) and apixaban (2 × 2.5 mg/d) as the only antithrombotic therapy.

Stent loss occurs more frequently in calcified lesions and/or significant proximal angulation. And this was also our case. We also used the common technique to remove the stent; however, in the end, it was not successful. Brilakis et al. [2] described the frequency of use of stent retrieval methods: advancing a balloon through the stent, inflating the balloon, and withdrawing the stent (45%); twisting two guidewires around the stent (5%); loop snare (26%); biliary forceps (12%); retriever (10%); or lasso/basket retrieval device (2%).

Interventional cardiologists should be familiar with a range of stent retrieval techniques. If they fail, interventional cardiologists must think creatively and be prepared to apply all equipment and expertise accessible in the cath lab to optimize the odds for positive outcomes and sometimes even use techniques reserved for vascular surgeons [3]. One must also remember that presently, with new-generation drug-eluting stents, there is a possibility to take a stent with a smaller nominal diameter (e.g., 3.5 mm) and easily postdilate it to the diameter of 4.5 and even 5.00 mm.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

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Intravascular ultrasound-guided reconstruction of chronic total occlusion true lumen after failed subintimal tracking and re-entry

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Subintimal plaque modification (SPM) (also termed as an "investment procedure") by subintimal tracking and re-entry (STAR) with subsequent balloon dilatation is a bailout strategy in failed chronic total occlusion (CTO) percutaneous coronary intervention (PCI) [1]. Little is known about the treatment of long-tract dissections resulting from unsuccessful SPM at follow-up.

A 74-year-old female with a history of diabetes mellitus presented with Canadian Cardiovascular Society class III angina. Transthoracic echocardiography showed preserved left ventricular ejection fraction. Coronary angiography demonstrated CTO of the proximal right coronary artery (RCA) with a blunt proximal cap and high tortuosity (J-CTO score 2) (Figure 1A, Supplementary material, *Video S1*). After failed CTO recanalization using antegrade wiring, controlled antegrade dissection and re-entry, and futile retrograde collateral crossing, the STAR technique was attempted in the distal RCA. Since the knuckle wire failed to re-enter into the true RCA lumen and went into the extraplaque position along the posterolateral artery, SPM was performed using a semi-compliant 3.0 mm balloon in the mid-to-distal RCA (Figure 1B, C, Supplementary material, *Videos S2, S3*). Angiography after 3 months showed a long-tract double-barrel dissection with obstructive residual stenosis in the distal RCA (Figure 1D, Supplementary material, *Video S4*). Based on the patient's persisting symptoms, the decision to reconstruct the RCA true lumen was undertaken. To this end, intravascular ultrasound (IVUS) was used for localization of the true lumen entry, and puncture using the Gaia Third guidewire (Asahi Intecc, Nagoya, Japan) was performed (Figure 1E, Supplementary material, *Videos S5, S6*). After IVUS confirmation of Gaia Third's intraluminal position, a double-lumen microcatheter was advanced through the entry site, and the posterior descending artery was successfully wired using the Sion Blue guidewire (Asahi Intecc, Nagoya, Japan) (Figure 1F, G, Supplementary material, *Video S7*). Following true-to-true lumen dilatation, repeated angiography and IVUS performed after 2 months showed complete resolution of RCA false lumen with Thrombolysis in Myocardial Infarction (TIMI) 3 flow (Figure 1H, I, Supplementary material, *Video S8*). The patient remained asymptomatic at 6-month follow-up.

The presence of false lumen dissections compromising distal coronary flow is not a benign complication of SPM at follow-up. Herein, we introduce the IVUS-guided antegrade wiring as a novel CTO PCI strategy for staged reconstruction of CTO true lumen after failed SPM in lesions with limited retrograde access.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

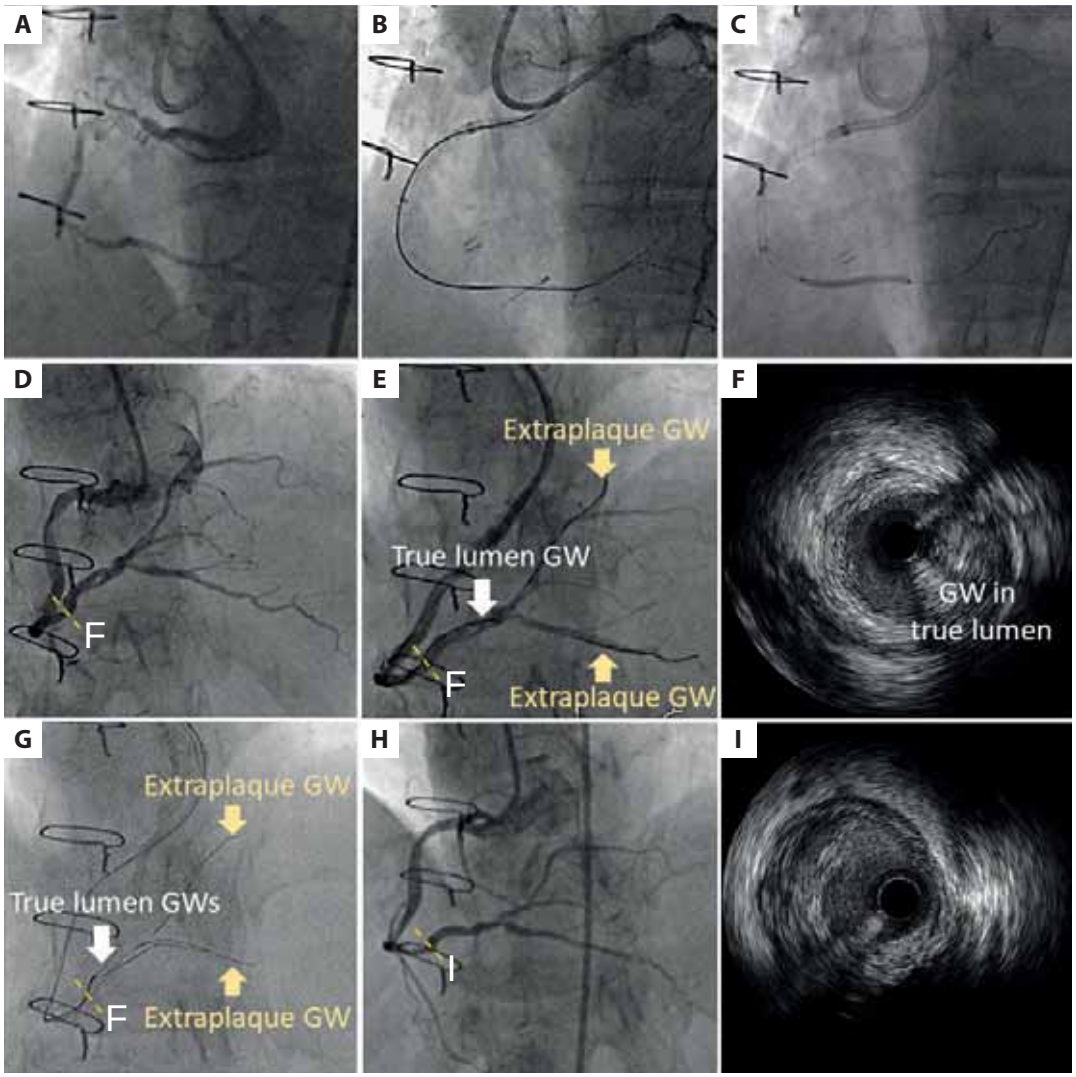

Figure 1. IVUS-guided antegrade wiring of the RCA true lumen after failed SPM. **A.** Baseline angiography showing CTO RCA. **B, C.** Failed subintimal tracking and re-entry with subsequent SPM in the distal RCA. **D.** Double-barrel RCA on control angiography. **E–G.** IVUS-guided puncture of the RCA true lumen using the Gaia Third guidewire and double-lumen microcatheter. **H, I.** Final angiographic and IVUS result with reconstitution of the RCA true lumen after 2 months

Abbreviations: CTO, chronic total occlusion; IVUS, intravascular ultrasound; GW, guidewire; RCA, right coronary artery; SPM, subintimal plaque modification

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Successful percutaneous transluminal angioplasty to treat superior vena cava syndrome

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Superior vena cava syndrome (SVCS) is caused by reduced blood flow through SVC, leading to facial and neck swelling, upper limb swelling, dyspnea and cough [1]. The most prevalent cause of SVCS is malignancy. The non-malignant causes include infection, thrombosis, and complications associated with intravascular devices. For example, 25% of patients with pacemakers have central venous obstruction, although only 1% of these patients are symptomatic, likely due to the development of collateral circulation [2]. Depending on the cause, the treatment of SVC includes radiotherapy or chemotherapy, systemic anticoagulation, or thrombolysis and endovascular techniques [2]. The latter include percutaneous transluminal angioplasty (PTA) and stenting [3], or thrombectomy [4]. Endovascular techniques have higher efficacy for symptom relief (80%–95%), compared to radiotherapy (56%–96%) and chemotherapy (59%–77%) [2], with a relatively low complication rate (0%–19%) [3]. We present a report on a patient with symptomatic SVCS, successfully treated with PTA.

A 34-year-old man with suspected arrhythmogenic cardiomyopathy, suspected Marfan syndrome, history of recurrent venous thromboembolism, triple sudden cardiac arrest, implantation of cardioverter-defibrillator (ICD) in secondary prevention, its triple removal and reimplantation (due to infection, end of battery life, and infective endocarditis) was admitted to the hospital due to stabbing chest pain and dyspnea. Upon physical examination, edema of the upper body and distended veins were observed, with no signs of peripheral congestion. Echocardiography showed normal dimensions and contractility of the left ventricle with ejection fraction of 50%, slightly dilated right ventricle, and moderate tricuspid regurgitation. Computed tomography angiography revealed an obstructed right brachiocephalic vein and subtotal occlusion of SVC with collateral circulation (Figure 1A; Supplementary material, *Video S1*). Symptomatic SVCS was diagnosed, and the patient was qualified for endovascular treatment.

Following the puncture of the right common femoral vein, digital subtraction angiography was performed from the left subclavian vein, confirming critical SVC stenosis (Figure 1B). Next, PTA was conducted using the EverCross Balloon Catheter (8 × 60 mm, 10 atm, Medtronic, Minneapolis, MN, US) and Atlas Dilatation Catheter (12 × 80 mm, 10 atm, Beckton Dickinson, Franklin Lakes, NJ, US) (Figure 1C). Control venography showed normal outflow of the SVC and no flow via the collateral circulation (Figure 1D; Supplementary material, *Video S2*). Following the procedure, SVC symptoms were alleviated within a few days. The ICD check confirmed correct device functioning. Considering the suspicion of arrhythmogenic cardiomyopathy and Marfan syndrome, genetic tests were scheduled.

Although malignancy remains the most prevalent cause of SVCS, the non-malignancy causes are increasing, including thrombus or obstruction due to repeated implantable cardiac device implantation [3]. In the case of thrombosis caused by COVID-19, successful rheolytic thrombectomy with AngioJet (Boston Scientific, Marlborough, MA, US) has

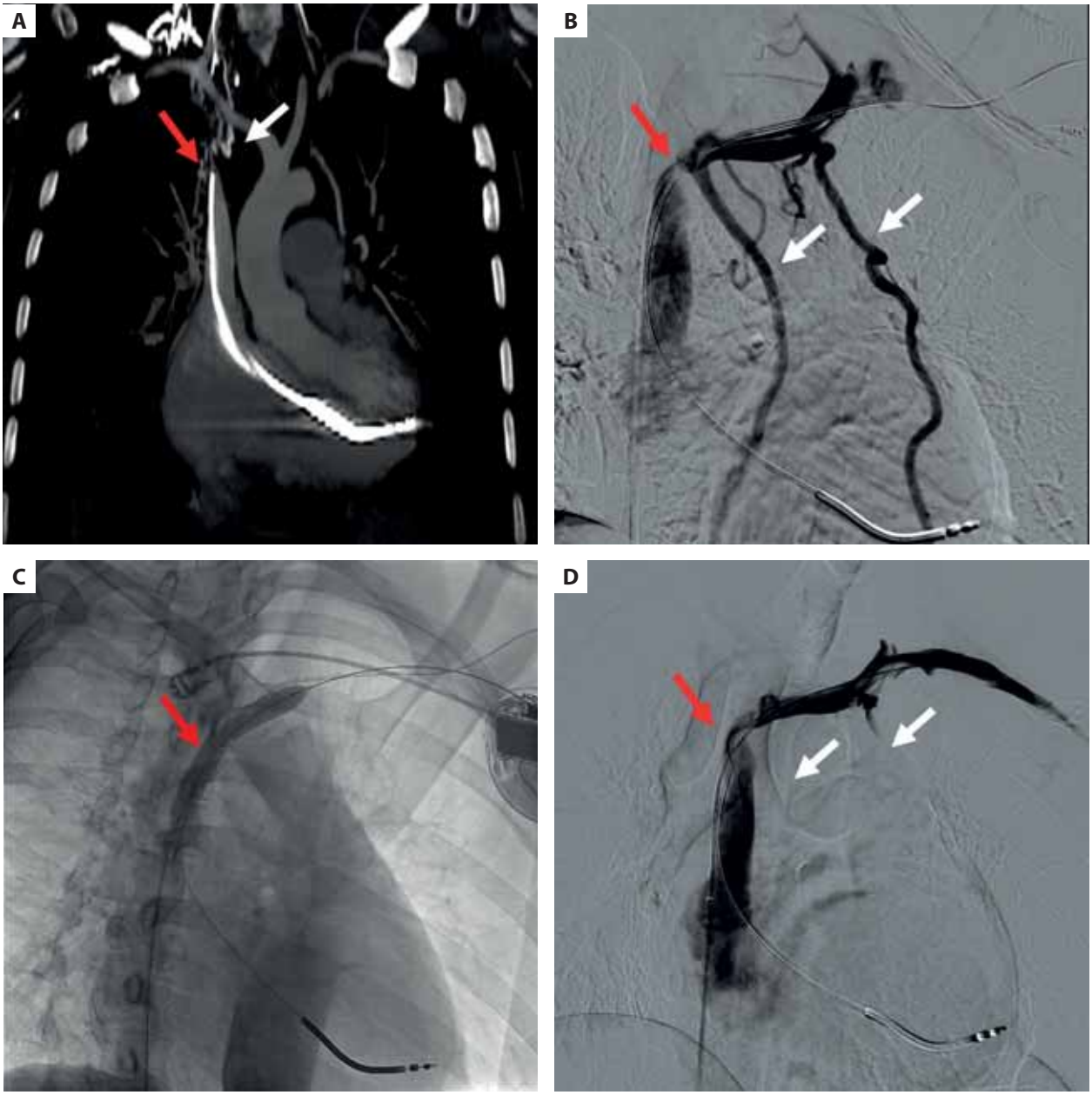

Figure 1. A. Computed tomography angiography showing the obstructed right brachiocephalic vein and subtotal occlusion of the superior vena cava (SVC; red arrow) with visible collateral circulation (white arrow); **B.** Digital subtraction angiography (DSA) showing critical stenosis of the SVC (red arrow) with visible collateral circulation (white arrows); **C.** Percutaneous transluminal angioplasty using the EverCross Balloon Catheter (8 × 60 mm, 10 atm, Medtronic); **D.** Control DSA showing normal outflow from the SVC, with no flow *via* collateral circulation (white arrows)

recently been reported; the device is also used for endovascular treatment of acute pulmonary embolism [4, 5]. In the case of intravascular devices, stent implantation, usually followed by oral anticoagulation, is the treatment of choice. Regarding the presence of the ICD wire in the SVC, history of infective endocarditis, and complete SVC expansion following PTA, no stent was implanted in this case. Since our patient had recurrent venous thromboembolism, he was chronically treated with dabigatran, which was continued after hospital discharge.

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

Article information

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Multiple late cardiovascular complications after combined oncological treatment of Hodgkin's lymphoma

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A 64-years-old female, actively smoking, with hypertension and dyslipidemia, was admitted to the department of cardiology for *de novo* retrosternal pain (Canadian Cardiovascular Society score II). In oncological history in 1992, the patient was diagnosed with Hodgkin lymphoma (HL) and treated with intensive head and chest radiotherapy (cumulative dose, 39 Gy). In 1998, a local relapse was noted and a successful COPP (cyclophosphamide, vincristine, procarbazine, prednisone)/ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy was administered. Physical examination revealed asymmetric pulse and difference in blood pressure between the upper limbs (43 mm Hg), with lower pressure, weakness, and numbness on the left one.

Computed tomography angiography of the chest documented inflammatory lesions, emphysema, minor nodular lesions without enlarged lymph nodes in the lungs, and severe calcification of the aorta, aortic branches, coronary arteries, and aortic valve. The ultrasound Doppler indicated non-significant stenosis of the left and right internal carotid arteries, stenosis of the left subclavian (LSA) and vertebral arteries (LVA), with stage III of subclavian steal syndrome. The diagnosis was confirmed on angiography, with 70% ostial stenosis of LVA with a highly calcified plaque in the LSA with collateral circulation (Figure 1A, B). It was established that angioplasty of lesions was not possible. The surgery of the LSA was delayed because of extensive neovascularization around the aortic arch and subclavian branches. The transthoracic echocardiography showed preserved contractility (left ventricular ejection fraction [LVEF], 55%), confirmed with global longitudinal strain, with hypokinesia of the basal segments of the lateral and inferior walls, and moderate tricuspid regurgitation. Moreover, a massively calcified aortic valve without significant stenosis was visualized. Furthermore, the post-exercise myocardial perfusion scintigraphy showed perfusion defects in the apical and septal segments (11% of the myocardium).

Coronary angiography demonstrated 80% stenosis of the left artery descending (LAD) and right coronary artery (RCA) (Figure 1C, D). Results were consulted with the Heart Team and the decision about staged primary percutaneous coronary intervention (PCI) was made due to the high risk of potential surgery complications resulting from the patient's history including chest irradiation. In the first step, LAD angioplasty with a semi-complaint balloon and stent implantation was performed (Figure 1E, F). PCI of the RCA was abandoned due to the extensive calcification and resolution of symptoms.

Currently, the number of cancer survivors and cardiovascular (CV) complications is constantly increasing [1]. In this report, we present a description of an HL survivor with multiple CV side effects, diagnosed almost 30 years after treatment. There are few similar descriptions of such CV complications in the literature [2]. The pathogenesis of these complications is mainly the microvascular destruction and vascular insufficiency caused by radiation-induced free radical generation and endothelial dysfunction caused

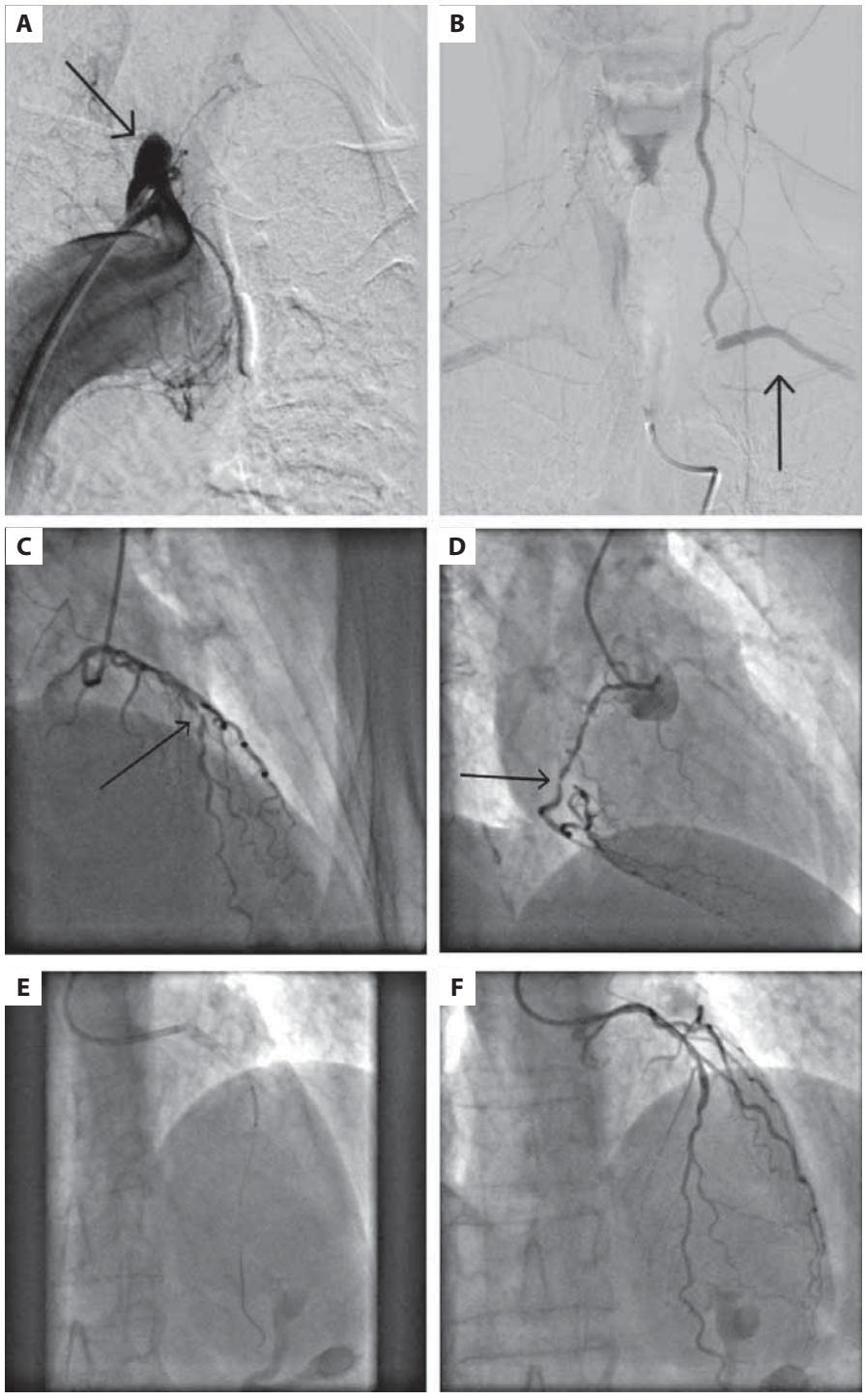

Figure 1. Angiography. **A, B**. 70% ostial stenosis of LVA with a significant highly calcified plaque in LSA with collateral circulation (arrow). **C.** Significant stenosis of LAD (arrow). **D.** 80% stenosis of RCA (arrow). **E.** LAD during PCI. **F.** The final effect of LAD PCI

Abbreviations: LAD, left anterior descending artery; LSA, left subclavian artery; LVA, left vertebral artery; PCI, percutaneous coronary intervention; RCA, right coronary artery

by anticancer agents in diverse molecular mechanisms that promote atherosclerosis and CV dysfunction [3]. In conclusion, the discussed patient had a high risk of their occurrence due to a high dose of applied non-selective chest radiotherapy (>30 Gy), a combination of hematological treatment methods as well as her young age during therapy, and several CV risk factors [4, 5]. Moreover, the currently recommended International Cardio-Oncology Society screening intervals enabling early detection of abnormalities and implementation of adequate preventive strategies (Supplementary material, *Figure S1*) were not applied [5].

Supplementary material

Supplementary material is available at https://journals.viamedica.pl/kardiologia_polska

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Unicuspid aortic valve: More data and more doubts in the light of six years of follow-up observation

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An unicuspid aortic valve is a rare congenital heart defect with an incidence is 0.02% [1, 2]. The optimal time for cardiosurgical treatment in young adults with congenital aortic valve disease may be a matter of controversy [3, 4]. In this population, left ventricle (LV) remodeling is an ongoing process from organogenesis onwards [5], and its degree may not match the severity of the defect.

We report a case of a 26-year-old male patient with a unicuspid aortic valve and consecutive diagnostic dilemmas in the interpretation of a discrepancy between left ventricular hypertrophy (LVH) and degree of unicuspid valve pathology during 6-year follow-up.

The unicuspid aortic valve was functionally incompetent. In 2016 both aortic regurgitation (AR) and stenosis (AS) were observed on transthoracic (TTE) and transesophageal echocardiography (TEE) (AR jet, 9 mm; PHT, 360 ms; V_{max}, 3.8 m/s; P_{mean}, 38 mm Hg; P_{max}, 57 mm Hg; AVA, 2.1 cm^2; bulb, 37 mm; AoAsc, 35 mm; AoDesc, 20 mm with normal flow and no signs of coarctation). Moreover, ~~a~~ significant concentric LVH was found (interventricular septum [IVS] up to 16 mm, posterior wall 18 mm) with normal systolic and diastolic diameters and preserved LV ejection fraction (LVEF, 67%) (Figure 1A–C). Additional clinical findings involved: a negative family history of hypertrophic cardiomyopathy (HCM); normal blood pressure (120/80 mm Hg), and normal kidney function (GFR above 90 ml/min/1.73 m^2). At discharge, further observation was indicated.

During the next hospitalization (2020), the patient did not present any limitations in physical activity (New York Heart Association [NYHA] class I, N-terminal pro-B-type natriuretic peptide [NT-proBNP], 117 pg/ml) and reported pain and paresthesia in the lower extremities. TTE/TEE showed mild progression of the aortic valve disease (AR jet, 10 mm; PHT, 310 ms; V_{max}, 4.2m/s; P_{mean}, 46 mm Hg; P_{max}, 67 mm Hg; AVA, 1.36 cm^2; bulb, 40 mm; AoAcs, 45 mm) and more advanced LVH (IVS, 21 mm; posterior wall, 19 mm) with LVEF of 65%. LV global longitudinal strain (GLS) was 15% with a typical pattern for amyloidosis. Cardiac magnetic resonance (CMR) confirmed LVH (Figure 1D) and LV hyperkinesis and multifocal intramuscular regions of late gadolinium enhancement. Given the progression of LVH symptoms and TTE results, other potent etiology etiologies of LVH were verified — both endomyocardial biopsy (hypertrophy and mild degree atypical reactive inflammation —Figure 1E) and biochemical/genetic tests were negative with regard to Anderson-Fabry disease, amyloidosis, or HCM. The patient was discharged with the recommendation of clinical and TTE control once a year.

In 2022 the still asymptomatic patient presented an increased NT-proBNP level (370 pg/ml), and more advanced signs of LV and aortic remodeling. Echocardiography showed LVH up to 20 mm, normal LV diameters, LVEF, 60%; LV GLS, 8.7% (Figure 1F), and the presence of an ascending aortic dilatation (bulb 40 mm, AoAsc 49 mm). The patient was qualified by Heart Team for surgical aortic valve replacement and ascending aortic surgery.

To conclude, the presented case shows that a unicuspid aortic valve may provide a complex form of valve structural and functional incompetence. Advanced LV remode-

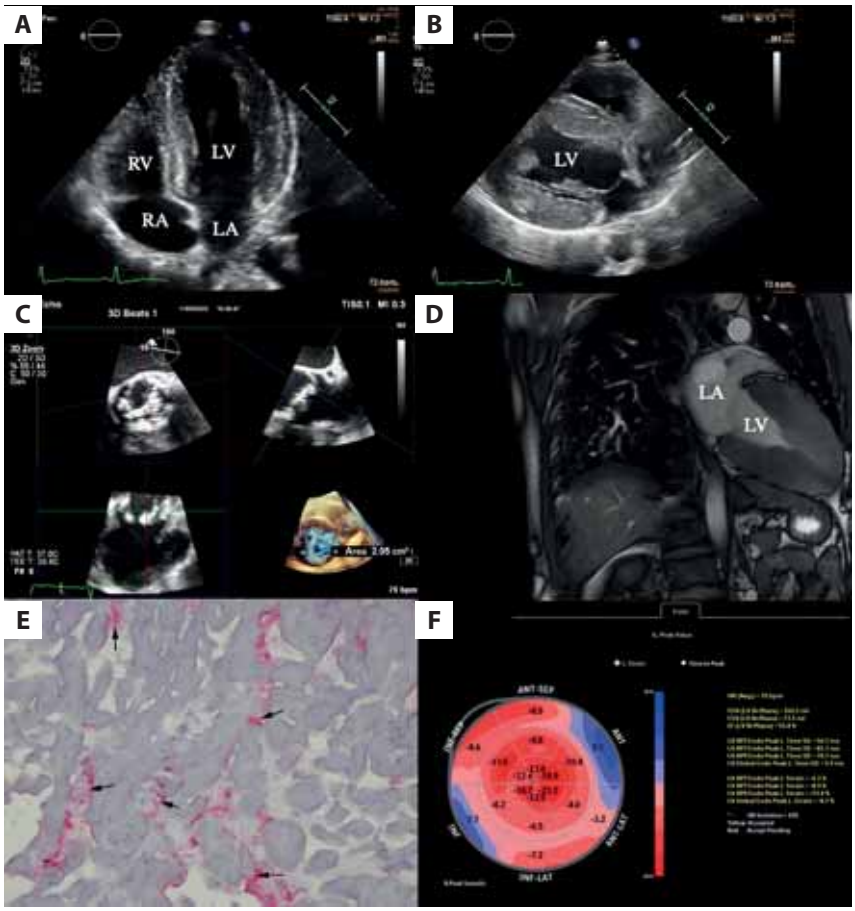

Figure 1. A. TTE, four-chamber view. **B.** TTE, parasternal long-axis view. **C.** TEE, 3D acquisition and multislice assessment of the aortic valve area. **D.** CMR with contrast. **E.** Endomyocardial biopsy demonstrated patchy distribution of CD68(+) macrophages (red color) with concomitant myocyte injury (arrows) suggesting reactive inflammation; **F.** LV GLS, 8.7%

Abbreviations: CMR, cardiac magnetic resonance; GLS, global longitudinal strain; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography

ling may pose some diagnostic problems. Moreover, the young age of the patient, atypical symptoms, and potent concomitant diseases make the decision about further treatment more complicated.

Article information

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Not such a benign entity. Cardiogenic shock and mechanical complication in a patient with working diagnosis of myocardial infarction with no obstructive coronary arteries

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An 82-year-old woman with a history of an ischemic stroke was admitted to the hospital with ST-segment elevation myocardial infarction complicated by pulmonary edema and cardiogenic shock (resistant to pharmacotherapy). Electrocardiography showed ST-segment elevation in the lateral leads and reciprocal denivelation in the inferior leads. Urgent coronary angiography demonstrated no significant coronary artery disease. Therefore, a working diagnosis of myocardial infarction with no obstructive coronary arteries (MINOCA) was made. Transthoracic echocardiography showed preserved left ventricular ejection fraction, akinesis of mid-lateral and mid-inferolateral segments of the left ventricle, severe acute mitral regurgitation (MR) due to flail leaflets and rupture of the head of the anterolateral papillary muscle (Figure 1A, B). This dramatic clinical manifestation prompted careful revision of coronary angiography images that disclosed proximal amputation of regressive ramus intermedius (because of the diameter of less than 1 mm a conservative approach was applied) (Figure 1C). Therefore, the ramus intermedius was assumed as an infarct-related artery (IRA).

The patient was urgently transferred to the cardiac surgery department. Intraoperative findings demonstrated almost total detachment of both mitral leaflets (Figure 1D); the patient underwent mechanical mitral valve replacement. Due to persistent severe circulatory and respiratory failure, the patient was hospitalized in the intensive care unit for nearly 3 months and unfortunately died of sepsis.

The diagnosis of MINOCA should be sequential, with careful assessment of the clinical context and exclusion of non-ischemic myocardial damage. Due to the heterogeneity of MINOCA patients, the diagnostic algorithm should be omnidirectional and include intracoronary imaging (intravascular ultrasound imaging, optical coherence tomography), cardiac magnetic resonance (CMR), and even intracoronary provocation tests in the investigation of coronary spasm and microvascular disease. However, before using advanced diagnostic tools (often invasive), it is recommended to re-review the angiographic images to detect overlooked obstructive coronary artery disease (CAD) [1]. In this case, the IRA was a small branch, but it supplied the crucial region of the myocardium. Acute ischemic MR resulting from papillary muscle head rupture is a life-threatening condition. The major treatment strategy is a surgical correction (mitral valve repair or valve replacement), characterized by high operative mortality (15.1% in comparison to 1.5% in chronic MR) [2].

Despite the data on better prognosis for patients with MINOCA compared to patients with myocardial infarction with obstructive coronary artery disease (MI-CAD), clinical presentation of MINOCA can be severe. In-hospital mortality in MINOCA patients amounts to 0.9%–1.1%, and 12-month mortality to 4.7%, which is even more worrying [3]. Therefore, patients with MINOCA require the same careful diagnostic and therapeutic approach as patients with MI-CAD.

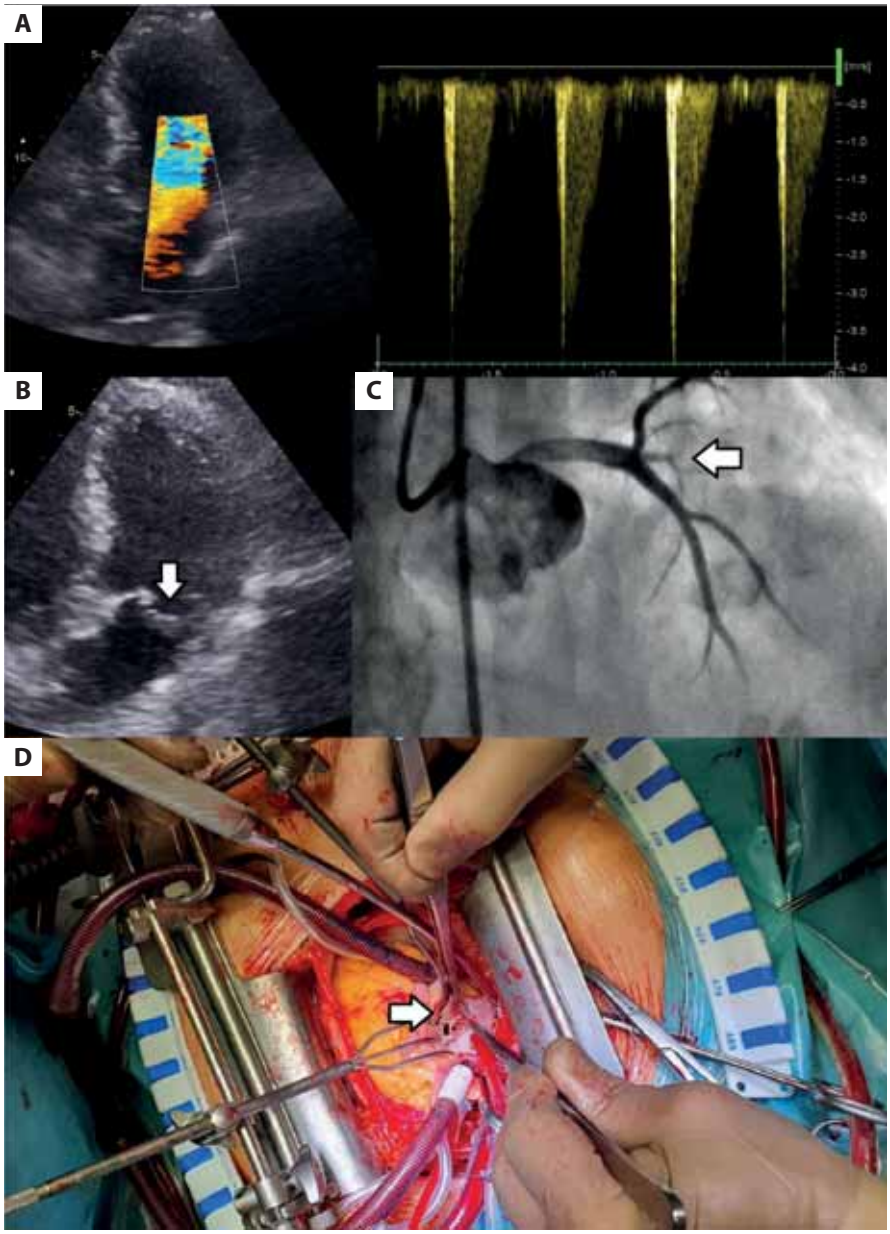

Figure 1. A. Four-chamber view transthoracic echocardiography: Doppler spectrum of acute severe mitral regurgitation. **B.** Four-chamber view transthoracic echocardiography: no coaptation because of flail leaflet (arrow). **C.** Proximal amputation of regressive ramus intermedius (arrow) found during revision of coronary angiography. **D.** Intraoperative image of the detached anterior mitral leaflet (arrow)

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Management of valvular heart disease in patients with cancer: Multidisciplinary team, cancer-therapy related cardiotoxicity, diagnosis, transcatheter intervention, and cardiac surgery. Expert opinion of the Association on Valvular Heart Disease, Association of Cardiovascular Interventions, and Working Group on Cardiac Surgery of the Polish Cardiac Society

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ABSTRACT

The Association on Valvular Heart Disease, Association of Cardiovascular Interventions, and the Working Group on Cardiac Surgery of the Polish Cardiac Society have released a position statement on risk factors, diagnosis, and management of patients with cancer and valvular heart disease (VHD). VHD can occur in patients with cancer in several ways, for example, it can exist or be diagnosed before cancer treatment, after cancer treatment, be an incidental finding during imaging tests, endocarditis related to immunosuppression, prolonged intravenous catheter use, or combination treatment, and nonbacterial thrombotic endocarditis. It is recommended to employ close cardiac surveillance for patients at high risk of complications during and after cancer treatment and for cancer treatments that may be cardiotoxic to be discussed by a multidisciplinary team. Patients with cancer and pre-existing severe VHD should be managed according to the 2021 European Society of Cardiology (ESC) and European Association for Cardio-Thoracic Surgery (EACTS) guidelines for VHD management, taking into consideration cancer prognosis and patient preferences.

Key words: cardiooncology, cancer, cancer therapy related cardiotoxicity, cardiovascular imaging, valvular heart disease

INTRODUCTION TO CARDIO-ONCOLOGY. CURRENT EUROPEAN SOCIETY OF CARDIOLOGY GUIDELINES

In the United States, the 5-year survival rate of cancer survivors reached 69% in 2022. Cardiovascular (CV) disease (CVD) is the most common cause of death in this population. The incidence of CVD and cancer increases with age. Moreover, the risk factors for CVD are the same as those for cancer. Therefore, with Europe and America facing the problem of population aging, it is increasingly common to see patients with both conditions.

The overarching goal of cardio-oncology is to assess CV toxicity risk during and after cancer treatment, including the risk of valvular heart disease (VHD). If cancer therapy-related CV toxicity occurs, the role of a cardiologist is to address all the CV needs of a cancer patient, so as not to interrupt specific anticancer treatment or to ensure that the interruption is as short as possible.

In patients with cancer, VHD can most often occur in the following clinical scenarios:

- VHD existing and/or diagnosed before cancer treatment or diagnosed as an incidental finding during imaging tests for cancer diagnosis
- endocarditis related to immunosuppression, catheter use, or combination treatment
- nonbacterial thrombotic endocarditis as the first possible symptom of cancer
- VHD caused by left ventricular (LV) dysfunction due to cancer treatment
- VHD caused by collagen accumulation as well as valvular fibrosis and calcification as late cardiotoxic effects of radiotherapy causing interstitial damage.

Irrespective of the underlying cause, the severity of VHD in patients with cancer is assessed using the same criteria as in patients without cancer.

In August 2022, the European Society of Cardiology (ESC) published its first guidelines on the management of CVD in patients with cancer [1]. The guidelines replaced or complemented the 2016 ESC position paper on cancer treatments and CV toxicity [2].

The main focus of the 2022 ESC guidelines is assessment of CV toxicity risk [1]. Pre-existing severe VHD is associated with high risk of cancer therapy-related CV toxicity in patients treated with anthracyclines, anti-human epidermal growth factor receptor 2 (HER-2) monoclonal antibody, and combination therapy with RAF and MEK inhibitors [1]. However, the reasons why pre-existing VHD is relevant in association with these cancer therapies remain unclear [1]. The presence of VHD itself may be associated with asymptomatic myocardial damage. This may be due to increased myocardial wall stress, which may lead to cardiac cell damage and subsequent cardiotoxicity. Moreover, severe VHD may cause an increase in baseline left ventricular ejection fraction (LVEF).

Therefore, close CV surveillance (cardiac imaging and biomarkers) is recommended in all patients at high risk of CV complications (including patients with VHD receiving the above cancer therapies) during and after cancer treatment, and cardiotoxic anticancer treatment should be discussed by a multidisciplinary team before starting treatment (class I, level C). Beta-blockers, angiotensin-converting enzyme inhibitors, and statins should be considered for primary prevention in patients at high CV toxicity risk, irrespective of VHD etiology (class IIa, level C) [1].

Echocardiography is recommended for assessment of cardiac function in all patients with cancer before treatment, with 3-dimensional echocardiography to assess LVEF and the measurement of global longitudinal strain if available (class I) [1].

Apart from the section on CV risk assessment (Table 1), the 2022 ESC guidelines [1] do not contain any specific recommendations for the management of patients with cancer and pre-existing VHD or new VHD during cancer treatment but refer to the 2021 ESC guidelines on the management of VHD [4].

Table 1. Adopted protocol for cardiovascular risk assessment in patients with cancer scheduled to receive cardiotoxic cancer therapies (e.g., anthracycline chemotherapy) based on reference [3]. Severe valvular heart disease — high risk

Medical history	Risk factor [Y/N]	Score	Level of evidence
Cardiovascular disease			
Heart failure or cardiomiopathy		Very high	B
Severe valvular heart disease		High	
Myocardial infarction or previous coronary revascularization		High	C
Stable angina		High	C
Baseline left ventricular ejection fraction <50%		High	B
Borderline left ventricular ejection fraction 50%–54%		Medium	C
Cardiac biomarkers			
Elevated troponin		Medium	C
Elevated NT-proBNP or BNP		Medium	C
Demographic or other risk factors			
≥80 years		High	B
65–79 years		Medium	B
Hypertension[a]		Medium	B
Diabetes mellitus[a]		Medium	C
Chronic kidney disease[a]		Medium	C
Current smoker or smoking history		Medium	C
Obesity (>30 kg/m^2)		Medium	C
Previous cardiotoxic cancer treatment			
Anthracycline exposure		High	B
Non-anthracycline chemotherapy		Medium	C
Left chest or mediastinum radiotherapy		High	C
SCORE: • low — no risk factors or 1 medium • medium — 2–4 medium risk factors • high — > medium risk factors or 1 high • very high — heart failure or cardiomiopathy			
[a]Blood pressure >140/90 mm Hg; HbAc1 >7.0% or > 53 mmol/mol or diabetes treatment; GFR < 60 ml/min/1.73 m^2			

Abbreviations: BMI, body mass index; BNP, B-type natriuretic peptide; GFR, glomerular filtration rate; HbA1C, glycated hemoglobin; NT-proBNP, N-terminal pro-B-type natriuretic peptide

Patients with cancer and pre-existing severe VHD should be managed according to the 2021 ESC/EACTS guidelines for the management of VHD, taking into consideration cancer prognosis and patient preferences (class I C).

Patients with cancer who develop new VHD during cancer treatment should be managed according to the 2021 ESC/EACTS guidelines for the management of VHD (class I C), taking into consideration cancer prognosis and comorbidities. However, the 2021 ESC/EACTS guidelines do not specifically address the management of patients with cancer [4]. Instead, they contain general recommendations that only indirectly refer to this complex population of patients. According to the guidelines, decision-making in patients considered for valve intervention should take into account estimated life expectancy and comorbidities, among other factors [4]. The guidelines recommend the Heart Team's discussion about benefits and risks of valvular surgery using popular risk scores. The Society of Thoracic Surgeons predicted risk of mortality score (STS-PROM) and the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) are recommended to discriminate between low- and high-risk surgical patients. However, only the STS-PROM incorporates previous mediastinal radiotherapy and a history of cancer.

In the 2022 ESC guidelines [1], specific recommendations for the cancer population with VHD are limited to patients with radiation-induced symptomatic severe valvular aortic stenosis (AS) at intermediate surgical risk. In these patients, transcatheter aortic valve implantation (TAVI) should be considered (class IIa, level B).

A multidisciplinary team (MDT) approach is recommended to discuss and determine the surgical risk in cancer survivors (class I, level C). MDT should include an oncologist, cardiologist with expertise in managing CVD in patients with cancer, invasive cardiologist, cardiac surgeon, anesthesiologist, and palliative medicine specialist.

Patients with cancer are usually poor candidates for classic cardiac surgery and should preferably be considered for minimally invasive procedures without extracorporeal circulation and transcatheter heart valve interventions [5, 6].

In 2021, more than 2000 TAVI procedures, 256 transcatheter mitral edge-to-edge repair (TEER) procedures, 29 percutaneous pulmonary valve implantation procedures, and 19 tricuspid valve interventions were performed in Poland. In 2021, 8294 heart valve surgeries were performed in Poland, including 7085 prosthetic valve implantations and 1744 valvular repair procedures. These numbers of procedures relate to all patients with VHD in Poland and include the population with cancer. All procedures, except tricuspid valve interventions, were reimbursed. The key aspect to consider in determining eligibility for the procedure is cancer prognosis (life expectancy >12 months).

Considering that the ESC guidelines on cardio-oncology put minimal emphasis on the specific population of patients with VHD receiving cancer treatment and contain only general recommendations, the present position statement seems to be particularly important.

Clinical assessment — summary

1. Each patient with cancer should be assessed for the presence of VHD.
2. Patients with known VHD should be assessed for previous cancer and cancer treatment.
3. Frequent CV surveillance is recommended in patients with VHD receiving cancer treatment (more frequent echocardiographic evaluation, measurement of biomarker levels [natriuretic peptides, cardiac troponins] than in patients without VHD).
4. The frequency of surveillance in patients at high and very high risk of CV toxicity is guided by the type of cancer treatment.
5. If significant VHD is diagnosed in patients with cancer, the treatment decision should follow a multidisciplinary team discussion.
6. A multidisciplinary team should include an oncologist, cardiologist with expertise in managing CVD in patients with cancer, invasive cardiologist, cardiac surgeon, anesthesiologist, and palliative medicine specialist.
7. The management strategy should take into consideration cancer prognosis and the patient's preferences and should be discussed with the patient.

DIAGNOSIS OF VALVULAR HEART DISEASE IN PATIENTS WITH CANCER

The use of imaging techniques for assessment of VHD in oncological patients largely follows the general recommendations for this disease entity developed by cardiology societies and expert groups. However, some specific circumstances should be considered in relation to the cancer process itself or side effects or complications of cancer treatment.

Echocardiography is the first-choice imaging technique for VHD diagnosis in all patients, including those with cancer [7]. Echocardiographic standards can be found in specific documents developed by the European Association of Cardiovascular Imaging and the American Society of Echocardiography [8, 9]. Although transthoracic echocardiography is often sufficient for assessing valvular lesions and related hemodynamic disturbances, transesophageal echocardiography (particularly 3D echocardiography) may offer a more detailed characterization of valvular pathology, providing a clear incremental value in infective endocarditis. It should be emphasized that transesophageal echocardiography can be performed only after the exclusion of esophageal cancer or related complications.

One should bear in mind that the quantitative assessment of valvular heart disease may be confounded by the cardiotoxic effect of anticancer drugs on left and right ventricular functions. Similarly, the interpretation of LVEF and global longitudinal strain (GLS) decision thresholds when assessing eligibility for valve intervention may be difficult in the presence of overlapping cardiotoxic effects of chemotherapy or radiotherapy. Due to the paucity of data on this subject in the available literature, a tailored imaging approach should be used in such cases.

Cardiac computed tomography (CT) and magnetic resonance imaging (CMR) are not routinely performed in assessment of valvular disease and are used as supportive tools. Cardiac CT is important in preprocedural planning of transcatheter and surgical valve replacement, including assessment of aortic root calcification, aortic valve calcium score, measurement of the valve annulus, coronary orifice height, and assessment of peripheral arteries for transcatheter interventions. CT can help identify complications of infective endocarditis, especially abscesses and pseudoaneurysms [10].

CMR can be used to quantify valvular VHD, especially regurgitation, when the quality of echocardiographic imaging is inadequate. This technique provides important prognostic information on the severity of myocardial fibrosis resulting from valvular disease and/or oncological therapies. CMR and CT can help investigate the etiology of masses on valvular structures, including differentiation of cancer tumors from thrombi [11].

Positron emission tomography (PET) can be used in the diagnosis of endocarditis on prosthetic valves [12].

Cardiac CT, CMR, and PET are important tools in diagnosis of carcinoid heart disease, providing information on the mechanisms of valve dysfunction (thrombosis vs. carcinoid deposits — CT and CMR) and identifying cardiac metastases (PET) [13].

Echocardiography is a safe technique, which is particularly important considering the need for serial testing as part of CV surveillance. CMR is also safe for patients, except for cases where metal elements are present in the body. A group of patients for whom this examination may be hazardous are women after the first stage of breast reconstruction with the use of tissue expanders due to the risk of dislodgement of the port [7]. Because of the exposure to ionizing radiation during CT and PET, the purposefulness of the use of these diagnostic techniques, despite a relatively low radiation dose from a single examination, should be carefully deliberated in oncological patients.

Diagnosis of valvular heart disease in patients with cancer — summary

1. Echocardiography is the first-line imaging test for the diagnosis of valvular heart disease. This also applies to the cancer population.
2. Echocardiographic evaluation should be performed in all patients before cancer treatment, if feasible, and novel techniques should be applied.
3. Cardiac CT is an important tool for planning transcatheter and surgical heart valve interventions. It may also

help identify infective-endocarditis-related complications, but radiation exposure should be considered.
4. CMR can be used to quantify VHD and the severity of myocardial fibrosis resulting from valvular disease and/or oncological therapies.
5. It should be noted that quantitative assessment of VHD may be confounded by the cardiotoxic effect of anticancer drugs on left and right ventricular functions.

PATIENTS DEVELOPING NEW VALVULAR HEART DISEASE AFTER CHEMOTHERAPY

In patients with active cancer or cancer survivors, new or worsening VHD may be related to chemotherapy, radiotherapy, or cancer-therapy-related CV events such as acute coronary syndrome, endocarditis, pulmonary hypertension, and mechanical prosthetic valve thrombosis.

Usually, two types of valvular dysfunction should be considered: (1) primary — structural dysfunction, which refers to alterations caused by damage to the components of the valve apparatus; and (2) secondary — functional dysfunction secondary to LV remodeling and enlargement as well as alterations in LV geometry. Another type of heart valve dysfunction occurs due to tumor invasion (most often myxoma), leading to functional narrowing of the valve orifice.

Cancer treatments can cause myocardial damage, LV remodeling, LV systolic dysfunction, and symptomatic heart failure (HF), which are described as cancer-therapy-related cardiac dysfunction (CTRCD). Cardiac dysfunction can be caused by various anticancer drugs acting via different mechanisms [14]. CTRCD thus encompasses a broad spectrum of clinical symptoms and morphological changes linked to the cardiotoxic effects of cancer therapies, including their impact on valve function. CTRCD with mitral and tricuspid valve dysfunction can be caused by classic cytostatic drugs, molecularly targeted cancer drugs, and immunomodulatory drugs. Secondary mitral and tricuspid regurgitation due to LV remodeling is a rare complication of radiotherapy, with structural alterations of the valve apparatus being more common.

The effect of chemotherapy on primary valve dysfunction is less well documented. Available literature data are conflicting, with some studies providing evidence for a link between valvular dysfunction and chemotherapy [14], and others reporting contradictory findings [15, 16]. The most likely complication of chemotherapy is secondary mitral and tricuspid regurgitation.

The management of patients with secondary mitral and tricuspid regurgitation associated with CTRCD is the same as that of patients with functional valve dysfunction of other etiologies. The mainstay of treatment is pharmacological management of HF (β-blockers, sodium-glucose cotransporter 2 inhibitors, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, sacubitril/valsartan, mineralocorticoid receptor antagonists, diuretics) [16]. Early initiation of medical therapy has a significant beneficial effect on survival, LV remodeling, and the severity of mitral regurgitation (MR) [17]. Also, cardiac resynchronization therapy was shown to reverse LV remodeling and reduce MR severity in patients fulfilling standard eligibility criteria [18]. Selected patients may be eligible for interventional treatment of severe MR.

Patients with new valvular heart disease after chemotherapy — summary

1. In patients with active cancer or cancer survivors, new or worsening VHD may be related to chemotherapy or cancer-therapy-related CV events such as acute coronary syndrome, endocarditis, pulmonary hypertension, and mechanical prosthetic valve thrombosis.
2. Treatment of CRTCD-related valve disease is the same as functional valve disease from other causes. The mainstay of treatment is pharmacological management of HF (beta-blockers, sodium-glucose cotransporter 2 inhibitors, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers, sacubitril/valsartan, mineralocorticoid receptor antagonists, diuretics).

PATIENTS WITH NEW VALVULAR HEART DISEASE AFTER RADIOTHERAPY

The main risk factor for VHD in patients subjected to cancer treatments is radiotherapy which causes damage to valvular tissues in close proximity to the radiation field. This mostly refers to patients with Hodgkin lymphoma or left-sided breast cancer who were treated with radiotherapy between 1965 and 1995 before the era of modern radiotherapy planning [19].

Radiation affects not only valvular tissues but also other tissues exposed to the radiation field. Therefore, radiation-induced VHD is usually accompanied by endocarditis, coronary and peripheral artery disease (atherosclerotic plaque formation in the aorta, neck, subclavian, axillary, and internal thoracic arteries), LV diastolic dysfunction (following myocardial fibrosis), restrictive cardiomyopathy, and conduction system disease (fibrosis of the conducting tissue) [20].

The pathomechanism of radiation-induced VHD has not been fully elucidated. Most likely, injury to valvular endothelial cells and interstitial cells of the endocardium leads to the onset of progressive "subclinical" inflammation as well as the release of cytokines and bone morphogenetic proteins, resulting in collagen accumulation, fibrosis, and calcifications [21]. The chronic inflammation process associated with cancer itself may further enhance the progression of valvular lesions. Radiation-related structural valve dysfunction occurs mainly after radiotherapy to the anterior and left side of the chest with exposure of the heart.

In the population that previously received mediastinal irradiation, the risk of valvular disease was 34-fold higher than in the Framingham population, which had never been subjected to radiotherapy [22]. The incidence of

Table 2. Risk factors for radiation-induced cardiovascular disease

High dose of radiation fractions and high cumulative dose of radiation
Longer radiation exposure time
Left chest irradiation location, a tumor in close proximity to the heart (exposure of the heart)
Pre-existing cardiovascular disease
Concomitant chemotherapy (anthracyclines)
Hypertension, dyslipidemia, diabetes, obesity, smoking

VHD increases with a longer time from radiation exposure. Clinically significant VHD was reported in 1% of patients at 10 years after radiotherapy; in 5%, after 15 years; and in 6%, after 20 years [8]. The incidence of cardiac lesions increased significantly at 20 years from exposure [23], with mild aortic regurgitation (AR) reported in 45% of patients; moderate AR, in 15%; AS, in 16%; mild MR, in 48%; and mild pulmonary regurgitation, in 12%. Tricuspid regurgitation is more common among adult survivors of childhood cancer than in the general population, but the reasons for this association remain unclear [24]. However, most patients with cancer have mild or moderate VHD that does not require surgical treatment. Severe VHD necessitating surgical intervention is rare.

The risk factors for radiotherapy-related VHD are presented in Table 2 [25].

Radiation-induced morphological changes in the valve apparatus

Radiation effects include valve leaflet fibrosis, thickening, calcification, and shortening as well as fibrosis, calcification, distortion, and degeneration of the mitral and aortic annulus and the ascending aorta, especially at the base. Fibrosis and calcification can present as diffuse foci and can be randomly dispersed or combined into extensive conglomerates.

Lesions in the mitral valve leaflet are usually located in the basal and middle segments while the apical segments near the coaptation line and the commissures do not show advanced damage [26, 27] (Figure 1). Such a distribution of lesions helps differentiate radiation-induced valve disease from a rheumatic disease characterized by degenerative lesions in the entire leaflets as well as commissural fibrosis and fusion [1].

Radiation-induced lesions are more common with left-sided valves (mitral and aortic). This is linked to the higher pressure in the left heart, which enhances radiation-induced microdamage. Valvular regurgitation is more common than stenosis. Aortic stenosis is more common than stenosis of other heart valves [28–30].

An unusual pattern of lesions in the aortic valve, mitral valve, and the aortic-mitral curtain is considered to be typical of radiation-induced valve disease [26] (Figure 2).

A characteristic feature is porcelain aorta, a term used to describe fibrosis and calcification of the ascending thoracic aorta (Figure 3).

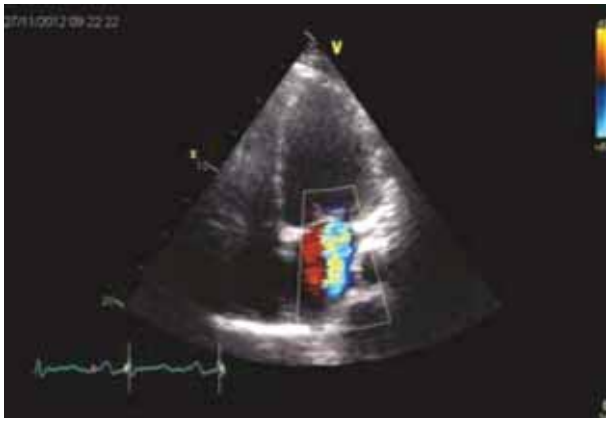

Figure 1. Mitral regurgitation after radiotherapy. Fibrosis found mainly in the mitral annulus and the basal segments of the mitral leaflets; minor lesions in the apical segments

The risk of clinically significant valvular disease is higher at radiation doses exceeding 30 Gy [31]. Notably, exposure to standard radiation doses of 20 to 30 Gy used in modern radiotherapy is associated with a low risk of VHD [32]. Some observations indicate that chemotherapy used before or during radiotherapy may increase the sensitivity of valvular tissue to radiation [1].

Echocardiography is the first-line modality for assessing radiation-induced valvular lesions. Typical echocardiographic features of radiation-induced VHD are presented in Table 3.

The recommendations for multimodality imaging evaluation of patients after radiotherapy were developed by the European Association of Cardiovascular Imaging and the American Society of Echocardiography in 2013 [25]. In all patients with prior exposure to anterior and left chest radiation, history-taking and physical examination should be performed annually to identify new heart and carotid murmurs, neurological signs and symptoms, symptoms of HF, and chest pain. Moreover, intensive measures should be taken to reduce CV risk factors. In asymptomatic low-risk patients, echocardiography 10 years after completion of cancer therapy and every 5 years thereafter is recommended. In high-risk patients (with prior exposure to anterior or left chest radiation and with at least one risk factor for cardiotoxicity), echocardiography should be performed no later than 5 years after radiotherapy, and noninvasive stress testing should be considered.

In patients with cancer, minimally invasive and transcatheter interventions are preferable due to increased bleeding risk, particularly in the setting of critical AS [5, 6]. In specific cases, TAVI for AR can also be considered [33].

Patients with cancer may present with mediastinal, pericardial, and pleural fibrosis as well as coronary artery disease following previous radiation exposure. Difficulties during surgery may also be related to frequent pericardial adhesions due to constrictive pericarditis, LV dysfunction, porcelain aorta, and pulmonary fibrosis [31, 34].

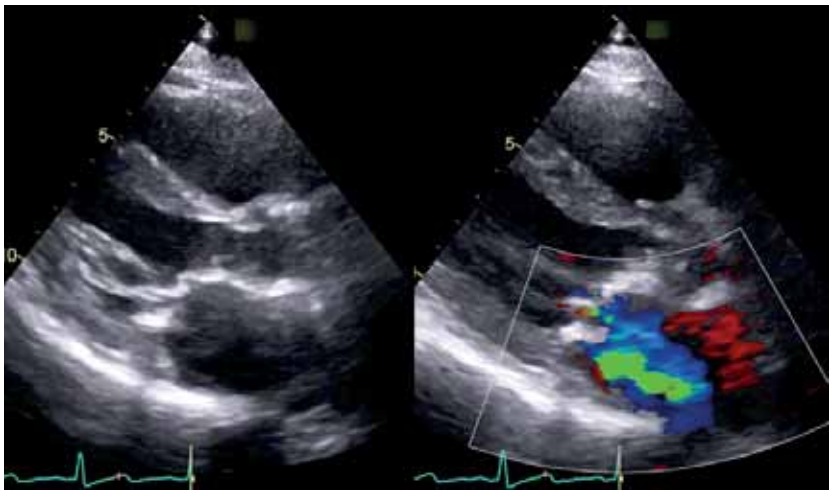

Figure 2. Radiation-induced valvular heart disease. Thickening of the aorto-mitral curtain. Moderate mitral regurgitation

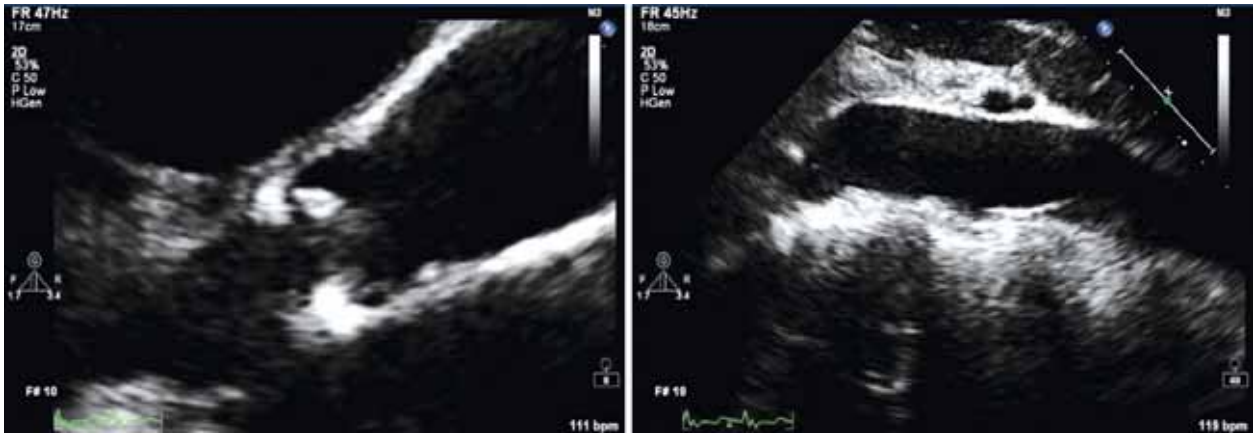

Figure 3. A. Aortic valve and ascending aortic calcification in an adult female patient 13 years after mediastinal radiotherapy for Hodgkin lymphoma. **B.** Similar calcification in the aortic arch (porcelain aorta)

Table 3. Echocardiographic features of radiation-induced valvular heart disease

Uniform valvular thickening due to fibrosis
Uniform distribution of lesions in the aorto-mitral curtain
Porcelain aorta
More severe lesions in left-sided valves (aortic, mitral) than in right-sided valves (tricuspid, pulmonary)
Regurgitation prior to stenosis
Fibrosis and calcification mostly of the base and mid portions of the valves; preservation of mitral commissural fissures

Patients with new valvular heart disease after radiotherapy — summary

1. In all patients with prior exposure to radiation, history-taking and physical examination should be performed annually to identify new heart and carotid murmurs, neurological signs and symptoms, symptoms of HF, and chest pain.
2. In patients after radiotherapy, intensive efforts should be made to reduce and treat CV risk factors.
3. In asymptomatic low-risk patients with prior radiation exposure, echocardiography 10 years after completion of cancer therapy and every 5 years thereafter is recommended.
4. In high-risk patients, echocardiography should be performed no later than 5 years after radiotherapy, and noninvasive stress testing should be considered.
5. High-risk patients are patients with previous exposure to anterior or left chest radiation and at least one risk factor (total radiation dose >30 Gy or 2 Gy/day; age <50 years; a tumor near the heart or an intracardiac tumor; concomitant chemotherapy with anthracyclines; presence of CV risk factors or known CVD).

TREATMENT OF VALVULAR HEART DISEASE IN PATIENTS WITH CANCER

Critical valve disease may be a contraindication to aggressive cancer treatment. This refers both to surgical treatment, with surgical risk increasing with the severity of VHD and to selected chemotherapy regimens. In such cases, priority is given to surgical valve repair, which should be done promptly, especially in patients with fast tumor growth and a relatively good prognosis. Considering the potential complications of chemotherapy (thrombocytopenia, coagulation disorders, immunosuppression, and susceptibility to infections), therapeutic strategies that do not require long-term anticoagulation or antiplatelet treatment should

be considered. Therefore, mechanical prosthetic valve implantation should be avoided, where justified, and bioprosthetic valve should be considered instead, especially since patients with cancer are usually at an older age and present with frailty and numerous comorbidities.

If the patient is at high surgical risk due to cancer or other biological causes, less invasive procedures should be considered, such as TAVI, balloon aortic valvuloplasty as palliative treatment, or — where justified — transcatheter mitral and tricuspid valve edge-to-edge repair. Minimally invasive procedures shorten recovery times, speed up urgent diagnostic workup, and reduce the waiting time for life-saving cancer treatment. Moreover, with minimally invasive procedures, extensive wounds can be avoided along with healing difficulties due to cancer itself and the use of chemotherapy and radiotherapy.

Palliative care patients with end-stage cancer and the quality of life determined by critical VHD constitute a specific population. The management of these patients is particularly challenging. They may require palliative treatment of VHD to improve the quality of life at the end of life. In the era of considerable advances in cancer treatment resulting in significantly longer survival, death in some cancer patients receiving palliative care may be caused by VHD rather than cancer. In these patients, valve replacement is not recommended because of poor outcomes and the high risk of classic cardiac surgery. Minimally invasive and percutaneous interventions such as palliative treatment are indicated. The risks and benefits of heart valve interventions should be carefully balanced, and medical futility should be avoided.

Effect of valvular heart disease on cancer treatment — summary

1. Significant VHDs, particularly stenosis, may be a contraindication to aggressive cancer treatment and may increase surgical risk. In such cases, priority is given to surgical valve repair, which should be done promptly, especially in patients with fast tumor growth and a relatively good prognosis.
2. In patients with VHD scheduled for chemotherapy (particularly with anthracyclines, HER-2, RAF/MEK), close and frequent monitoring (echocardiography, biomarkers) is indicated during and after treatment.
3. Considering potential chemotherapy-related complications (thrombocytopenia, coagulation disorders, immunosuppression, susceptibility to infection), therapeutic strategies that do not require long-term anticoagulation or antiplatelet treatment should be considered (mechanical prosthetic valve implantation should be avoided).
4. If the patient is at high surgical risk due to cancer or other biological causes, less invasive procedures should be considered, such as TAVI, balloon aortic valvuloplasty as palliative treatment, or – where justified – TEER.
5. TAVI should be considered in patients at intermediate surgical risk with symptomatic AS caused by radiotherapy.

TRANSCATHETER AORTIC VALVE INTERVENTION IN PATIENTS WITH CANCER

AS is the most common acquired heart disease in elderly patients, and older age is also associated with an increased incidence of cancer. Patients who underwent mediastinal radiotherapy at a younger age for the treatment of malignancy (e.g. breast cancer, lung cancer, lymphoma) are at risk of late cardiotoxicity manifesting as aortic and mitral valve fibrosis. The risk of VHD is significantly higher at radiation doses exceeding 25 Gy [25, 35] or 30 Gy [31]. Radiation-induced valvular calcifications are extensive and affect numerous surrounding structures, including the aortic annulus, subvalvular apparatus, and the aorto-mitral curtain. Calcification of the aorto-mitral curtain is considered a typical complication of cardiac radiation exposure, and severe calcification is a strong predictor of mortality in patients undergoing cardiac surgery.

The adverse effects of radiotherapy affect not only the aortic valve but also a significant portion of the ascending aorta together with the branches of the aortic arch. Almost 60% of such patients develop significant atherosclerosis of the ascending aorta, while porcelain aorta is seen in about 15% of patients [36]. Severe calcification of the ascending aorta may preclude cardiac surgery. At the same time, endovascular aortic procedures remain feasible but are associated with higher risk of complications, such as stroke or peripheral embolism. Patients with severe AS and previous radiotherapy are at higher long-term mortality risk after surgical aortic valve replacement (SAVR) than those without previous radiotherapy [36]. The higher short-term and long-term risk may be caused by worse pulmonary ventilation due to radiation-induced pulmonary fibrosis, the need for simultaneous mitral valve replacement and coronary artery bypass grafting, as well as fibrosis of the pericardial and right ventricular free wall.

Surgical risk assessment in patients with cancer poses a significant challenge. Surgical risk scores are limited because they do not include a history of cancer or previous chest radiation. According to the 2017 ESC guidelines for the management of VHD, the decision between SAVR and TAVI in patients with risk factors such as frailty, porcelain aorta, or previous chest radiation should be guided by the Heart Team discussion and follow a careful assessment of the individual patient. TAVI is preferable in patients when transfemoral access is possible, especially in those at older ages [37]. The more recent 2021 guidelines generally recommend TAVI if comorbidities preclude SAVR [4]. Current data on SAVR vs TAVI in patients with previous chest radiotherapy come from small retrospective studies or subanalyses of larger studies [38]. Therefore, each patient after chest radiotherapy requires a personalized approach.

The most recent ESC guidelines on cardio-oncology recommend that patients with severe AS are managed according to current clinical knowledge while considering cancer-related prognosis. TAVI should be considered in patients with symptomatic radiation-induced AS and intermediate surgical risk (class IIa) [1].

Another important aspect is the management of patients with severe symptomatic AS and newly diagnosed cancer. Compared with TAVI, cardiac surgery with extracorporeal circulation may significantly delay cancer treatment. Therefore, the treatment choice should be based on the risk-benefit assessment and individualized based on cancer stage and prognosis. TAVI will be a more common strategy in this scenario because it reduces recovery time and delays in starting cancer treatment. Therapeutic decision-making should consider the higher risk of surgical complications in patients with cancer due to higher rates of hemostatic disorders such as thrombocytopenia, coagulopathy, or hypercoagulation. In selected cases, patients with relatively good long-term prognosis (at least 1-year survival after cancer treatment) may be considered for balloon aortic valvuloplasty (BAV) as a bridge to definitive valve repair. Temporary hemodynamic improvement after BAV reduces the risk of cancer surgery. Usually, aortic valve replacement, most often TAVI, can be safely performed a few weeks after BAV [39]. In patients with poor cancer-related prognosis and severe symptomatic AS, BAV can be performed as a palliative treatment to improve the quality of life [40].

TRANSCATHETER HEART VALVE INTERVENTIONS IN PATIENTS WITH CANCER: MITRAL, TRICUSPID, AND PULMONARY VALVES

The presence of VHD is associated with increased risk of perioperative CV complications in patients undergoing noncardiac surgery (NCS), such as cancer surgery [41]. As described in the section on the management of patients with VHD undergoing NCS, the mode of treatment depends on the type of valve disease, urgency of NCS, and the risk of perioperative complications [42]. Also, in patients with cancer treated with medical therapy (cytostatic drugs, biological drugs) or radiotherapy, the choice of valve disease treatment should be guided by efforts to minimize the risk of death and HF as well as to improve the quality of life without exposing the patient to the excessive risk associated with the intervention. Cardiac surgery in these patients may be challenging, particularly with previous chest radiotherapy (fibrosis, delayed wound healing, and higher risk of infection, including endocarditis). Transcatheter valve repair and replacement seem to be the safest option for these patients. An important consideration is the need for anticoagulant and antiplatelet treatment after valve repair/replacement. Anticoagulation and antiplatelet treatment can increase the bleeding risk in patients with drug-induced or radiation-induced coagulopathies (bone marrow suppression, increased risk of gastrointestinal bleeding). Antiplatelet treatment in patients with cancer is associated with a 1.6-fold higher bleeding risk compared with patients without cancer. It seems justified to avoid the combination of oral anticoagulation and dual antiplatelet therapy. Good communication among the MDT members is essential [43].

Transcatheter mitral valve edge-to-edge repair

Eligibility: (1) the presence of HF symptoms in patients with severe primary MR not eligible for surgical valve repair and fulfilling criteria suggesting an increased chance of responding to the treatment; (2) HF symptoms despite optimal medical therapy and cardiac resynchronization therapy according to the ESC guidelines for the management of HF in patients with moderate or severe MR fulfilling criteria suggesting an increased chance of responding to the treatment (COAPT inclusion criteria); (3) patients not fulfilling all the clinical criteria but who may derive clinical benefit from mitral TEER as per the Heart Team's judgment [4]. In conclusion, the presence of cancer itself should not constitute a contraindication to TEER unless the estimated life expectancy is less than 12 months. Reduction of HF symptoms can improve the quality of life and facilitate cancer treatment [1].

The technique is similar to standard transcatheter valve repair, but extra caution is advised when obtaining vascular access in patients with thrombocytopenia or coagulation disorders. Ultrasound-guided femoral puncture, frequent monitoring of activated clotting time during the procedure (recommended value of about 300 s), and maintenance and frequent monitoring of hemostasis (at least two hemostatic systems should be considered, i.e., vascular suture and hemostatic suture [a figure-of-eight suture] or two vascular systems) are recommended. The atrial septal puncture should be guided by transesophageal echocardiography to reduce the risk of tamponade.

The choice of medical therapy after the procedure should consider the benefits (prevention of thromboembolic complications in patients with atrial fibrillation [AF]) against the risks (bleeding). In the absence of a high bleeding risk, standard medical therapy is recommended (antithrombotic treatment with non-vitamin K antagonist oral anticoagulants [NOACs]) in patients with indications for long-term anticoagulation plus an antiplatelet drug for 1 to 3 months or dual antiplatelet therapy for 1 month, with one of the drugs maintained for 3 to 6 months. In patients at high bleeding risk with indications for anticoagulation, the treatment should be limited to NOACs and a single antiplatelet therapy for 3 months. However, these recommendations are not based on evidence from randomized controlled trials [1].

Transcatheter tricuspid valve edge-to-edge repair

Eligibility: symptoms of right HF in inoperable patients with severe tricuspid regurgitation (TR) fulfilling anatomical criteria, when the clinical benefit of the procedure is

expected according to the Heart Team evaluation. Specific cases include patients with TR associated with carcinoid syndrome, where a decision on TEER should be based on a multidisciplinary team discussion, including life expectancy as assessed by the treating oncologist. As in mitral TEER, the technique is similar to standard transcatheter valve repair, except that a higher risk of bleeding complications can be expected in patients with right HF and secondary liver failure. Medical therapy after the procedure should follow the same criteria as for mitral TEER. Interventions that are unlikely to result in clinical improvement should be avoided (severe right ventricular dysfunction, systolic pulmonary artery pressure [SPAP] >70 mm Hg) [4].

Transcatheter interventions in pulmonary valve disease

The eligibility criteria for transcatheter interventions in patients with pulmonary valve disease and cancer are the same as for patients without cancer. The key considerations include reducing the risk of bleeding complications during the procedure and assessment of potential benefits in life expectancy, clinical status, and quality of life [4].

HEART VALVE SURGERY IN PATIENTS WITH CANCER

Both cancer survivors and those with active cancer may require heart valve surgery.

It was estimated that from 2% to 4% of patients undergoing heart valve surgery were previously treated for cancer. Most patients (70%–80%) presented with solid cancer (mainly breast, large intestine, prostate, and bladder cancer), while hematological malignancies were less common. Previous chemotherapy is generally not associated with increased surgical risk unless chemotherapy-related cardiotoxicity results in permanent cardiac damage. Knowledge of specific treatment-related side effects facilitates an appropriate surgical risk assessment. Cancer therapy-related CV toxicity, as well as the potential for reversibility, was summarized in the 2022 ESC guidelines on cardio-oncology [1].

Also, previous radiotherapy has implications for heart valve surgery, especially in the case of radiation to the chest. The side effects of radiotherapy that should be considered before surgery include pericarditis (with possible pericardial adhesions or effusion) and myocardial and pulmonary fibrosis. Other important aspects include radiotherapy-induced injury to the internal mammary artery used as a conduit for revascularization procedures as well as injury to the aortic and mitral valves themselves, which may adversely affect the repair. Radiation-induced CV toxicity can also include aortic pathology, such as aortic wall calcification (porcelain aorta), which may significantly limit, or even preclude, the cross-clamping procedure or even extracorporeal circulation. The risk of radiation-induced CV toxicity is higher in patients receiving higher radiation doses and young patients. Importantly, radiotherapy can also cause esophageal fibrosis, which increases the risk of esophageal perforation during perioperative transesophageal echocardiography. In patients with previous radiotherapy, chest CT for pulmonary and CV assessment should be an indispensable part of the preoperative planning or even the Heart Team/MDT decision-making.

In patients with active cancer, the decision on management strategy should be based on multidisciplinary team discussions involving a cardiologist, cardiac surgeon, interventional cardiologist, oncologist, and anesthesiologist. The most important factor to be considered in the decision-making process is life expectancy. Valve surgery is usually unwarranted if cancer is associated with shorter expected survival than VHD. According to the ESC/EACTS guidelines [4], heart valve surgery in patients with symptomatic VHD is not indicated if no improvement in the quality of life can be expected or if life expectancy is less than 12 months. In patients with a good cancer prognosis, the most important aspect to consider is which procedure to perform first (oncological or cardiac surgery), bearing in mind that cardiac surgery will most likely delay cancer treatment by about 1 month. Based on the ESC and European Society of Cardiac Surgery guidelines, non-cardiac cancer surgery (NCOS) is safe in asymptomatic patients with VHD, including those with severe disease. The presence of symptoms or LV dysfunction should prompt consideration of valvular surgery before cancer surgery, but NCOS can be performed first, especially in patients with valvular regurgitation.

Concomitant cancer and cardiac surgery can also be considered. Good outcomes of concomitant surgery were reported in case-series studies, particularly in patients with lung and gastrointestinal cancer. If lung resection is performed simultaneously with cardiac surgery, the thoracic part of the procedure is usually performed first. Relatively good outcomes of a combined approach were reported for minor cancer surgery (stage I or II lung cancer, partial gastrectomy) and relatively good cardiac function. In the case of more advanced cancer, major surgeries, and more advanced CVD, cardiac surgery should be performed first, followed by cancer surgery.

Notably, both cancer treatment and cancer itself are often linked with a prothrombotic state. Cancer often induces the release of tissue factor and other factors that can indirectly activate factor X. Myeloproliferative neoplasms, such as chronic myeloid leukemia, are also associated with higher risk of disseminated intravascular coagulation. Therefore, appropriate thromboprophylaxis is an important consideration in the perioperative management of patients with cancer.

Notably, unequivocal evidence to support a link between cardiac surgery with extracorporeal circulation and the risk of cancer spread is lacking.

In conclusion, a multidisciplinary approach to the management of patients with cancer, with careful consideration of the above factors and planning of the subsequent stages of treatment, is important for individual patient outcomes.

MINIMALLY INVASIVE/ROBOT-ASSISTED PROCEDURES FOR VALVULAR HEART DISEASE IN PATIENTS WITH CANCER

The most common cause of heart valve intervention in patients with cancer is the progression of pre-existing VHD, previous endocarditis, and LV remodeling. As mentioned before, radiotherapy-induced fibrosis and calcification most often affect the aortic valve leaflets, followed by the mitral valve leaflets, but also the aorta, mediastinum, and pericardium, which is associated with a higher surgical risk [8, 26, 44–46].

Minimally invasive procedures, including robot-assisted procedures, are possible in highly specialized centers. Considering pre-existing CVD in patients with cancer, minimally invasive procedures seem to offer a greater benefit.

The gold standard for aortic valve and ascending aortic surgery is upper mini-sternotomy, in which an incision is made only in the upper one-third of the sternum. This approach provides good access to the aortic valve, allowing valve replacement or repair. It also spares the lower two-thirds of the sternum, which helps maintain shoulder girdle stability and facilitates rehabilitation. In a selected group of patients, this surgery can also be performed through right anterior mini-thoracotomy. In this technique, sternal incision is not required, and access is obtained by small incisions and openings in the intercostal space. Patients who undergo right anterior mini-thoracotomy can be mobilized and rehabilitated already on the first day after surgery [47]. Minimally invasive procedures can also be performed in patients with mitral and tricuspid valve disease. Mitral and tricuspid valve surgeries are performed using right lateral mini-thoracotomy or a full thoracoscopic approach. In most patients, the skin incision is done at places where scars occur naturally, for example, around the nipple in men. This makes the surgical scar almost invisible. In centers specializing in minimally invasive cardiac surgery, such procedures are performed with 3D technology, which uses high-resolution equipment and increases procedural precision. The use of 3D glasses allows the surgeon to access views from inside the chest [48].

So far, the robotics technology has been the greatest achievement in the field of minimally invasive surgery. However, it requires considerable experience. In robot-assisted surgeries, there is no need to do an incision, and transthoracic access is obtained via skin ports into which the robot arms are introduced. Such surgeries are unique in that the surgeon-operator is not present at the operating table but sits at the robot console and performs the procedure by navigating the robot's arms inside the chest (Figure 4). The advantage of robot-assisted surgeries over thoracoscopy is the extraordinary mobility of the robot's arms. The arms have a very wide field of view and can reach locations that are unattainable with a thoracoscope [49].

Minimally invasive and robot-assisted procedures shorten recovery and hospital stay; they also reduce postoperative pain. Other benefits include a less frequent need for blood products, reduced incidence of arrhythmia, and in some populations, lower mortality rates [50]. The sternal-sparing approach is also associated with lower risk of severe local infections. Also, a shorter recovery time helps prevent infections (e.g., lung infection that is frequently observed in these patients). Finally, faster recovery reduces the time between cardiac surgery and subsequent cancer therapy.

MANAGEMENT OF PATIENTS WITH VALVULAR HEART DISEASE SCHEDULED FOR ONCOLOGIC SURGERY

The risk of perioperative CV complications is higher in patients with known VHD. The highest risk is observed in patients with AS and mitral stenosis (MS). The risk increases with the severity of VHD and depends on the type of planned surgery. According to Glance et al. [41], in most cases, NCOS is associated with intermediate or high risk of CV death, thus the presence of VHD may be problematic in a significant number of patients with cancer.

Compared with open surgery, endoscopic procedures are associated with lower complication rates, reduced fluid shifts, and better postoperative pulmonary ventilation, which is important in patients with VHD. Thus, it is important to consider these factors when deciding on the access site.

Echocardiographic evaluation is recommended in all patients scheduled for elective intermediate- or high-risk NCOS to determine the type and severity of VHD. The association of clinical symptoms with VHD and cancer stage should be assessed (class I, level C) [42].

In patients with severe VHD, time-sensitive surgery should be performed with close hemodynamic monitoring, and decisions on elective NCOS should consider the presence of VHD-related symptoms and CV comorbidities (coronary artery disease, reduced LV systolic function). A surgical risk assessment by the Heart Team should consider the patient's preferences and should be communicated to the surgical team. In general, severe symptomatic MS or AS should be treated before both time-sensitive and elective NCOS because they are associated with the highest CV risk. If NCOS can be safely delayed, the repair of severe AR and MR with concomitant HF should be considered.

Severe aortic stenosis

The key aspects to consider in patients with severe AS scheduled for elective NCOS include clinical symptoms, LVEF, and coronary artery disease. Eligibility is determined using the same criteria as in patients without planned NCOS. The measurement of biomarkers (NT-proBNP and troponin) may be useful in asymptomatic patients or in the presence of atypical symptoms. Symptomatic patients scheduled for intermediate- or high-risk NCOS should undergo SAVR or TAVI (according to the 2021 ESC/EACTS

Figure 4. Robot-assisted surgery with the Da Vinci robot (Intuitive Surgical, Sunnyvale, CA, US)

guidelines for the management of VHD) (class I, level C) [4]. In patients scheduled for time-sensitive NCOS, TAVI should be considered. In patients at high risk of valve replacement, with the presence of contraindications, with lack of consent to cardiac surgery, or in need of time-sensitive NCOS, BAV may be considered as a bridge to definitive valve repair (class IIb, level C). In asymptomatic patients with severe AS and preserved LVEF, low- and intermediate-risk NCOS can be safely performed. Similarly, in asymptomatic patients with LVEF <50%, low- and intermediate-risk NCOS can be safely performed with perioperative hemodynamic monitoring.

Severe mitral stenosis

In patients with mild MS (valve area >1.5 cm^2) or in asymptomatic patients with moderate to severe MS (valve area ≤1.5 cm^2) and SPAP <50 mm Hg, NCOS is associated with low CV risk.

In asymptomatic patients with moderate to severe MS and SPAP >50 mm Hg and in symptomatic patients with MS, percutaneous mitral commissurotomy (PMC) or valve surgery is recommended before high-risk NCOS (class I, level C). Low- and intermediate-risk NCS in asymptomatic patients with severe MS can be performed with appropriate perioperative hemodynamic monitoring if PMC is unfeasible due to valve morphology.

Aortic regurgitation

Patients with mild to moderate AR can undergo NCOS at no additional CV risk. In symptomatic patients with severe AR or asymptomatic patients with severe AR eligible for valve intervention, the intervention is recommended before elective intermediate- or high-risk NCOS (class I, level C).

Mitral regurgitation

In patients with symptomatic severe primary MR or asymptomatic severe primary MR with LV dysfunction, surgical or transcatheter valve intervention should be considered before elective intermediate- or high-risk NCOS (class IIa, level C).

In patients with severe secondary MR who remain symptomatic despite optimal medical therapy, surgical or transcatheter valve intervention should be considered before NCS (class IIa, level C).

In patients with AR or MR with significantly reduced LVEF, peri- and postoperative monitoring with a special focus on rate and fluid control is recommended to optimize cardiac output and reduce MR severity.

Transcatheter valve interventions in patients with cancer — summary

1. In patients referred for time-sensitive NCOS, TAVI should be considered in patients with severe AS.
2. In patients at high risk of valve replacement, with contraindications, lack of consent to cardiac surgery, or in need of time-sensitive NCOS, balloon aortic valvuloplasty may be considered as a bridge to definitive valve repair.
3. In asymptomatic patients with severe AS and preserved LVEF, low- and intermediate-risk NCS can be safely performed. Similarly, in asymptomatic patients with LVEF <50%, low- and intermediate-risk NCOS can be safely performed with perioperative hemodynamic monitoring.
4. In asymptomatic patients with moderate to severe MS and SPAP >50 mmHg and in symptomatic patients with MS, PMC or valve surgery is recommended before high-risk NCOS.
5. In symptomatic patients with severe AR or in asymptomatic patients with severe AR eligible for valve intervention, the intervention is recommended before elective intermediate- or high-risk NCOS.
6. In patients with symptomatic severe primary MR or asymptomatic severe primary MR with LV dysfunction, surgical or transcatheter valve intervention should be considered before elective intermediate- or high-risk NCOS.
7. In patients with severe secondary MR who remain symptomatic despite optimal medical therapy, surgical or transcatheter valve intervention should be considered before NCOS.

Heart valve surgery in patients with cancer — summary

1. In patients with previous radiotherapy, chest CT for pulmonary and CV assessment should be an indispensable part of the preoperative planning.
2. Notably, unequivocal evidence to support a link between cardiac surgery with extracorporeal circulation and the risk of cancer spread is lacking.
3. Minimally invasive and robot-assisted procedures shorten recovery and hospital stay; they also reduce postoperative pain. Sternal-sparing procedures also reduce the risk of severe local infections.
4. When determining eligibility for surgery, estimated life expectancy/prognosis as well as the risk-benefit ratio should be considered.
5. Surgical risk can be assessed using the STS-PROM score, as it considers previous chest radiotherapy and previous cancer (as opposed to other risk scores).

MANAGEMENT OF AORTIC DISEASE IN PATIENTS WITH CANCER

Management of patients with aortic dilatation

Cancer treatment in patients with thoracic aortic dilation (ascending aorta diameter, 35–55 mm; descending aorta diameter, 35–60 mm) is the same as in patients without aortic disease, and thoracic aortic dilatation is not a contraindication to conservative treatment (chemotherapy or radiotherapy) or surgical treatment. Each patient with aortic dilatation and hypertension should receive oral β-blockers (if not contraindicated) as the only oral drugs that reduce the dp/dt ratio, thus lowering the risk of acute aortic syndrome. Some chemotherapeutics used for cancer treatment can significantly increase blood pressure and the risk of acute aortic syndrome (acute aortic dissection, aortic rupture, intramural aortic hematoma). This particularly refers to angiogenesis inhibitors. Patients receiving such medications should be closely monitored for blood pressure, and aggressive antihypertensive treatment should be administered if needed. Increased blood pressure is observed only during cancer treatment and can be successfully managed with antihypertensive drugs.

Aortic dilatation ranging from 45 to 55 mm for the ascending aorta and from 50 to 60 mm for the descending aorta is associated with only slightly higher risk of acute aortic syndrome and is not a contraindication to cancer treatment and should not delay such treatment. If conservative or surgical cancer treatment is required, blood pressure should be closely monitored, aggressive antihypertensive treatment should be started, and the patient should be instructed to avoid heavy physical activity, especially isometric training. During the delivery of anesthesia for surgery, blood pressure should be monitored, preferably with invasive blood pressure monitoring, which offers a more precise real-time measurement. During surgery, blood pressure should not be higher than 130 mm Hg.

Management of patients with aortic aneurysms

The management of patients with an aortic aneurysm (ascending aorta diameter >55 mm or descending aorta diameter >60 mm) and cancer requires an individualized approach. The decision on treatment strategy should follow a multidisciplinary team discussion involving an oncologist, cardiologist, and cardiac surgeon. The decision should be based on assessment of:

- The risk of surgical aortic aneurysm repair
- The size and site of aortic aneurysm
- The risk of cancer treatment and its cardiotoxicity
- Cancer prognosis.

The final decision should always take into consideration patients' preferences and their willingness to accept higher-risk treatment.

In patients with smaller aortic aneurysms, it is possible to avoid surgical treatment so that cancer treatment is not delayed. The risk of acute aortic syndrome is higher with larger aneurysms. Therefore, in patients with large aneurysms (>6 cm for the ascending aorta), surgery should be performed before cancer treatment. In-vitro and in-vivo studies showed that extracorporeal circulation can cause significant immunosuppression. Despite previous concerns, there is no evidence that extracorporeal circulation is associated with cancer spread or increased cancer progression and mortality. The need for rehabilitation after cardiac surgery may delay cancer treatment. Patients with cancer are at higher risk of severe complications during and after surgery.

Management of patients with Stanford aortic dissection

Ascending aortic dissection is a life-threatening condition requiring emergency surgery. In patients with cancer, the decision on the management strategy should be made immediately based on all the available data and with consideration of the patient's preferences. If technically feasible, minimally invasive interventions should be considered, including endovascular procedures. In patients with cancer with a poor prognosis or at very high surgical risk due to poor clinical status, a decision not to perform surgical repair can be considered. Each patient with aortic dissection should be closely monitored and receive aggressive antihypertensive treatment.

Management of patients with aortic aneurysms — summary

1. The management of patients with aortic aneurysms (ascending aorta diameter >55 mm or descending aorta diameter >60 mm) and cancer requires an individualized approach. The decision on treatment strategy should follow a multidisciplinary team discussion involving an oncologist, cardiologist, and cardiac surgeon.

INFECTIVE ENDOCARDITIS AND NONBACTERIAL THROMBOTIC ENDOCARDITIS IN PATIENTS WITH CANCER

The reported incidence of cancer in patients with infective endocarditis (IE) ranges from 5.6% to 17.6%. It is more prevalent in men and elderly patients. Patients with IE may either have active cancer or previous cancer history although this is not always reflected in studies [51–54].

Infective endocarditis is more common in patients with cancer than in the general population. This may be due to immune disorders and prothrombotic state as well as the need for numerous invasive diagnostic and therapeutic procedures (e.g., catheters, central ports, various devices) that increase susceptibility to bacteremia (port of entry), including IE. Other causes include a higher risk of local and systemic infections, elderly age, and a higher incidence of CV comorbidities, including pre-existing VHD. Immunosuppression is also affected by the type of cancer (blood cancer, metastases) and the type of cancer treatment. Nevertheless, the prevention of endocarditis in patients with cancer should follow the same guidelines as in the general population. In particular, it is limited to preventive measures before oral procedures, even though invasive procedures constitute the port of entry for bacteria [51].

In patients with cancer, IE is associated with higher mortality and can adversely affect treatment outcomes, for example, by prompting a decision not to use or to delay chemotherapy or to modify aggressive treatment. In patients with cancer, IE can have atypical clinical presentation as compared with patients without cancer, characterized by less frequent fever, a new heart murmur, and a higher risk of complications such as acute kidney failure with subsequent thrombotic events and HF [51, 53, 54].

In patients with cancer, IE affects mainly the mitral and aortic valves. The most common causative pathogen, also associated with the worst prognosis, is Staphylococcus aureus, followed by *Enterococcus*. On the other hand, IE caused by *Streptococcus gallolyticus* (previously *S. bovis*) and *Enterococcus fecalis* was associated with a higher incidence of colorectal cancer or neoplasms. Therefore, colonoscopy is recommended in these patients [55–57], and IE may be an early marker of colorectal cancer and other types of cancer [52, 57]. IE is more common in elderly patients with colorectal, lung, and prostate cancer, as compared with individuals without cancer. Although gastrointestinal and lung cancer, as well as hematological malignancies, were linked to IE, specific management strategies are lacking [53].

Patients with advanced cancer may develop nonbacterial thrombotic endocarditis. This particularly refers to lung cancer, pancreatic cancer, and gastrointestinal adenocarcinomas. Valvular vegetations in nonbacterial thrombotic endocarditis are usually small (<1 cm), have an irregular shape, and typically involve left-sided valves. Vegetations are found on damaged and undamaged valves but may also involve the tendinous cords, left atrial appendage, and the remaining endocardium. In these patients, nonbacterial thrombotic endocarditis usually leads to embolic events in the central nervous system or another important organ [52, 58, 59].

The diagnosis of IE in patients with cancer is the same as in patients without cancer. Echocardiography is the first-line imaging modality as the safest method with no radiation exposure. The role of CT, PET/CT, and CMR is also emphasized. However, differentiation between inflammatory, cancer, metastatic, and thrombotic lesions remains challenging or even unfeasible [59, 60].

Patients with IE and treatable cancer should receive guideline-based empiric antibiotic therapy depending on the type and location of the microorganism as well as the

type of cancer treatment. Research shows that patients with IE and cancer are more often treated with amoxicillin, ceftriaxone, and daptomycin than with vancomycin [53, 54].

Indications for surgical treatment of IE in patients with cancer are the same as in patients without cancer. Mortality at 1 year in patients with cancer was higher than in patients without cancer (18.0% vs. 10.2%; P <0.001), and the risk factors included creatinine levels higher than 2 mg/dl, HF, and no surgery despite indications [54]. Bioprosthetic valves were more common in patients with cancer versus those without. However, it was reported that cardiac surgery is less often performed in patients with cancer despite indications [51, 54], and this is also linked to higher mortality rates in patients with IE and cancer. Pugalenthi et al. [53] argued that cardiac surgery should be performed in patients with treatable cancer (with no metastases) in the absence of contraindications. This is supported by the fact that some malignancies (i.e., prostate, breast, and colorectal cancer) are often associated with long survival [58]. On the other hand, often the reason why surgery is not performed is not cancer itself but other factors such as surgical risk, patient's death, or the lack of consent [53].

A recent algorithm for the management of patients with IE and cancer suggests that in patients with previous or current treatable cancer with no metastases, IE should be treated according to the guidelines, irrespective of the causative pathogen. In the remaining cases, medical therapy is recommended. If IE is caused by S. Gallolyticus or Enterococcus, colonoscopy is recommended [54].

Infective endocarditis and nonbacterial thrombotic endocarditis in patients with cancer — summary

1. In patients with cancer, IE can have atypical clinical presentation as compared with patients without cancer, characterized by less frequent fever, a new heart murmur, and a higher risk of complications such as acute kidney failure with subsequent thrombotic events and HF.
2. In patients with cancer, IE affects mainly the mitral and aortic valves. The most common causative pathogen, associated also with the worst prognosis, is Staphylococcus aureus, followed by Enterococcus.
3. Patients with advanced cancer may develop nonbacterial thrombotic endocarditis. This particularly refers to lung cancer, pancreatic cancer, and gastrointestinal adenocarcinomas.
4. Indications for antibiotic and surgical treatment of IE in patients with cancer are the same as in patients without cancer.

CARDIAC TUMORS WITH VALVULAR INVOLVEMENT

Cancer significantly affects the natural course of pre-existing VHD [61, 62]. On the other hand, chemotherapy (CTRCD) and radiotherapy adversely affect the valvular structures, accelerating degeneration and increasing susceptibility to IE.

Carcinoid tumor is a type of malignancy that directly affects valvular morphology and function. It is a neuroendocrine tumor that releases serotonin and is found in the liver or the ovary [61]. Increased amounts of serotonin are released consequent to impaired serotonin degradation by liver cells due to metastatic liver involvement. In 20% to 50% of patients, carcinoid tumor causes heart damage, usually VHD, with myocardial metastases or pleural effusion being less common. Carcinoid heart disease more often involves right-sided valves (typically the tricuspid valve) than left-sided valves. This is because monoamine oxidase in the lungs degrades serotonin limiting its release into the circulation. However, in patients with patent foramen ovale, concomitant atrial septic defect, hormonally active tumor in the lungs, or poorly controlled carcinoid syndrome, the involvement of the left-sided valves is also observed (one-third of patients with carcinoid heart disease). Valve damage is caused by serotonin, which stimulates valvular myofibroblasts to excessive collagen and glycosaminoglycan production by acting on the serotonin receptors 5-HT2B. This leads to the thickening of valvular leaflets and subvalvular apparatus, with the formation of carcinoid plaque. The typical feature is the absence of calcified foci in the valvular structures. In terms of morphological lesions, carcinoid syndrome causes increased regurgitation with retracted and immobile leaflets. The main cause of death in patients with carcinoid syndrome is right HF due to endocardial fibrosis of the right ventricle and volume overload following severe tricuspid or pulmonary regurgitation.

The prognosis of patients with carcinoid heart disease has improved after the introduction of somatostatin analogs and new surgical techniques for liver metastases. In patients with well-controlled symptoms and metastatic foci and with a cancer prognosis longer than 12 months, tricuspid valve replacement is recommended (class I). The choice between bioprosthetic and mechanical valves should be guided by individual patient and disease characteristics, as both types of valves have their pros and cons in carcinoid heart disease. The decision on surgery should follow a multidisciplinary team discussion (cardiologist, cardiac surgeon, anesthesiologist, oncologist, endocrinologist) and should take into consideration the risk of carcinoid crisis among other factors (class I, ESC guidelines) [61, 62].

Tumors that directly affect the heart valves include papillary fibroelastoma, and less commonly, myxoma and metastatic tumors [61, 63]. Papillary fibroelastoma is a mild tumor that constitutes about 11.5% of all primary cardiac tumors and three-fourths of all tumors associated with valvular dysfunction. The tumor is composed of elastic fibers and collagen with an endothelial covering. It is attached to the endocardium of the aortic and mitral valves (less commonly the tricuspid valve) by a short connective tissue pedicle. In contrast to vegetations, fibroelastomas

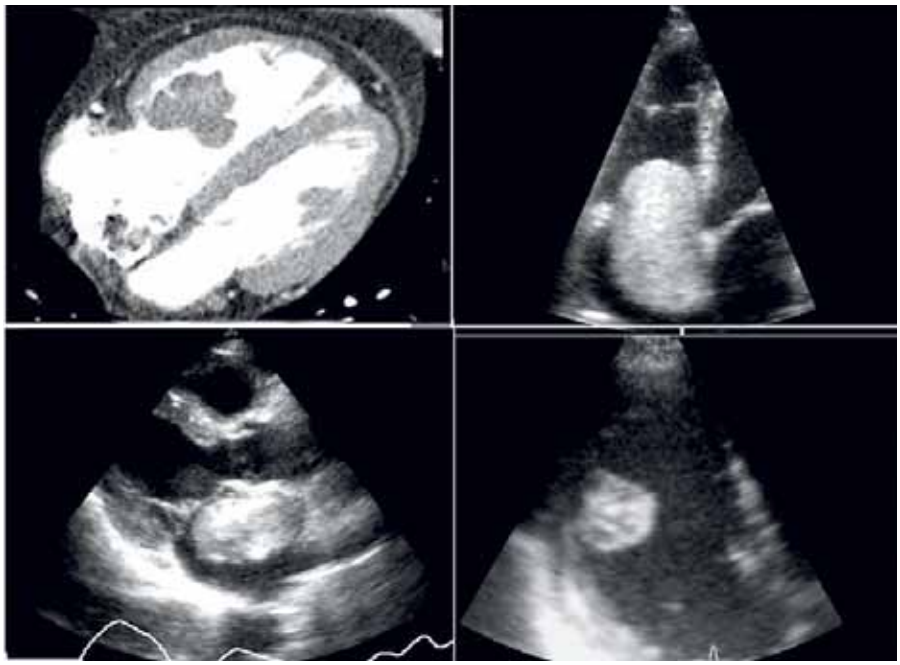

Figure 5. Changes in the topography and morphology of cardiac myxomas. **A.** A tumor with ragged "cluster-of-grapes" appearance in the inflow portion of the right ventricle, partially connected to the subvalvular apparatus of the tricuspid valve (contrast-enhanced CT). **B.** A large cylindrical pedunculated tumor narrowing the orifice of the tricuspid valve. **C.** Left atrial tumor limiting mitral leaflet mobility. **D.** Pedunculated lobular tumor in the left atrial appendage

are found on the ventricular side of the mitral valve or the aortic side of the aortic valve. Fibroelastomas usually do not cause valvular dysfunction, but patients may present with neurological complications following left-sided peripheral embolism. Due to its small size, characteristic "sea anemone" appearance, and free movement on the pedicle, papillary fibroelastomas are not easily identified on transthoracic and transesophageal echocardiography. If the results are inconclusive, CT and magnetic resonance imaging should be used as additional diagnostic tests.

Surgical treatment of papillary fibroelastoma is recommended for tumors greater than 1 cm in diameter and found on the left-sided valves in patients at low surgical risk or during cardiac surgery for other indications. Tumors on the tricuspid and pulmonary valves are usually treated conservatively unless they block the orifice or pose a risk of paradoxical embolism (leaky heart valve). If the patient is ineligible for surgical treatment, antiplatelet therapy should be considered [63].

Myxoma is the most common mild cardiac tumor (about 30% of all mild primary cardiac tumors). Although myxoma does not directly involve the valve structures, it may lead to atrioventricular valve dysfunction when located in the atria. This most often leads to functional stenosis with all the hemodynamic sequelae of mitral and tricuspid stenosis. Myxoma usually occurs as a single tumor. In 75% of cases, it is found in the left atrium; in 15%, in the right atrium; and in 5%, in the left and right ventricles (Figure 6 [64]). Multiple sites are rare. The characteristic feature of myxoma is its connection with one is correct the interatrial septum via a mobile pedicle. The tumor surface is usually regular and smooth but often has a rugged "cluster-of-grapes" appearance with a tendency for fragmentation and the risk of embolism. There are two types of myxoma: sporadic and familial (about 5%–10% of cases). Compared with sporadic tumors, familial myxomas more often have multiple foci, are more often found in the ventricles, and have higher recurrence rates. Familial myxomas may be associated with Carney syndrome that encompasses multiple myxomas in the heart and other locations, endocrine disorders, skin pigmentation, thyroid cancer, and Sertoli cell tumors of the testis. In most cases, an initial diagnosis of myxoma and its hemodynamic consequences can be made by transthoracic and transesophageal echocardiography. The tumor location in the right heart may necessitate additional CT, especially if peripheral embolism is the dominant clinical symptom. In each case of a suspected cardiac myxoma, surgical resection should be performed. The final diagnosis is made on the basis of histopathological findings. Considering high recurrence rates, patients after surgical resection should be followed with regular echocardiographic assessment.

ANTICOAGULATION IN PATIENTS WITH CANCER AND VALVULAR HEART DISEASE

The incidence of VHD, particularly degenerative valve disease, increases with age. Also, cancer is more prevalent among elderly patients and is associated with a worse prognosis. The management of patients with cancer and VHD constitutes a considerable challenge. Evidence-based guidelines that could facilitate therapeutic decision-making are lacking. Patients with cancer who also have VHD, AF, and a history of heart valve interventions require long-term or short-term anticoagulant and antiplatelet treatment.

There is limited evidence on anticoagulation in patients with cancer. Known factors to be considered in anticoagulation decisions in this population include the use of non-vitamin K antagonist oral anticoagulants (NOACs);

thrombocytopenia, which is common in cancer patients and increases bleeding risk; drug-drug interactions; intracerebral and liver metastases; low protein levels; eating disorders caused by nausea, vomiting, and anorexia; and interruptions of medical therapy due to invasive procedures [65].

Atrial fibrillation is common in patients with VHD, and it can also be induced by cancer drugs. Research shows that the CHA2DS2-VASc score, a standard tool for predicting the risk of thromboembolism in patients with AF, provides different results for patients with cancer versus those without. Therefore, the CHA2DS2-VASc score should be used with caution, and treatment should be individualized and take bleeding risk into consideration [66]. In patients with AF and moderate or severe MS, as well as in those with mechanical prosthetic valves, anticoagulation with vitamin K antagonists (VKAs) guided by the international normalized ratio (INR) is indicated. In the remaining patients with AF, the few available studies confirm the safety of anticoagulation with NOACs. NOACs are preferable to VKAs or heparins in patients with newly diagnosed AF who receive chemotherapy, except for patients with gastrointestinal cancer and noninvasively treated primary tumors or active gastrointestinal mucosal lesions [67]. In emergencies, such as a time-sensitive surgery or life-threatening bleeding, anticoagulation treatment should be discontinued immediately. The effects of dabigatran can be reversed with a specific reversal agent – idarucizumab. Andexanet alfa, a reversal agent for all direct factor Xa inhibitors and selected indirect factor Xa inhibitors (unfractionated heparin, low-molecular-weight heparin [LMWH], and fondaparinux) is currently unavailable in Poland. In patients receiving rivaroxaban and apixaban, fresh frozen plasma or prothrombin complex concentrate can be used. In patients on VKAs, vitamin K, fresh frozen plasma, or prothrombin complex concentrate are used.

In patients with low platelet count (25–50 × 109/l), half-dose LMWH can be used, and platelet transfusion can be considered. In patients with platelet count <25 × 109/l, individualized treatment is indicated.

The number of patients with prosthetic heart valves and concomitant cancer has been increasing. Anticoagulation in these patients differs depending on the type and location of the valve. The most recent 2021 ESC/EACTS guidelines on the management of VHD recommend lifelong anticoagulation with VKAs guided by the INR in patients with mechanical prostheses. During the perioperative period, bridging with unfractionated heparin or LMWH can be used. There is evidence on the use of a therapeutic dose of LMWH as bridging therapy in patients with increased thrombocytopenia or thrombocytosis or increased bleeding risk. However, the safety of this strategy was not confirmed in randomized controlled trials [68]. The ESC/EACTS guidelines recommend strict anti-factor Xa monitoring to ensure optimal LMWH dosing, which may help balance the risks against the benefits in patients with cancer. Anticoagulation with NOACs is not recommended in patients with mechanical prostheses.

Bioprosthetic valves do not require long-term anticoagulation, irrespective of the position. Current guidelines recommend VKAs during the first 3 months in all patients with bioprosthetic mitral or tricuspid valves. In patients after bioprosthetic aortic valve surgery, acetylsalicylic acid (75–100 mg/d) or a VKA in the first 3 months should be considered. After 3 months, NOACs, rather than VKAs, are indicated in patients with AF and surgical bioprosthesis.

Patients with cancer have a higher thrombotic and bleeding risk. Therefore, decisions on interventions requiring anticoagulant or antiplatelet treatment may be quite challenging. Factors to be considered in a multidisciplinary team discussion include the hemodynamic status of the patient as well as the type and stage of cancer. If recommendations on management are lacking, an individualized approach is warranted. TAVI is a common procedure in patients with AS and cancer. Lifelong single antiplatelet therapy is recommended in patients after TAVI without indications for oral anticoagulation. Immunosuppressive therapy was not associated with a higher rate of vascular access complications or CV events in patients during a short-term (median, 567 days) and long-term (6 months to 5 years) follow-up [69, 70].

All patients with cancer requiring anticoagulant or antiplatelet treatment should undergo regular assessment for thromboembolic and bleeding risk, which may change over time.

Anticoagulant and antiplatelet treatment — summary

1. There is limited evidence on anticoagulation in patients with cancer. Known factors to be considered in anticoagulation decisions in this population include the use of direct oral anticoagulants; thrombocytopenia, which is common in cancer patients and increases bleeding risk; drug-drug interactions; and intracerebral and liver metastases.
2. In patients with low platelet count (25–50 × 10^9/l), half-dose LMWH can be used, and platelet transfusion can be considered. In patients with platelet count <25 × 10^9/l, individualized treatment is indicated.
3. Lifelong single antiplatelet therapy is recommended in patients after TAVI without indications for oral anticoagulation. In the presence of indications for oral anticoagulation, anticoagulant monotherapy is recommended, except for patients with coronary stent implantation <3 months before TAVI. In such cases, a combination of anticoagulant and antiplatelet treatment is recommended.
4. Patients with mechanical prosthetic valves should receive lifelong anticoagulation with VKAs guided by INR monitoring.

Article information

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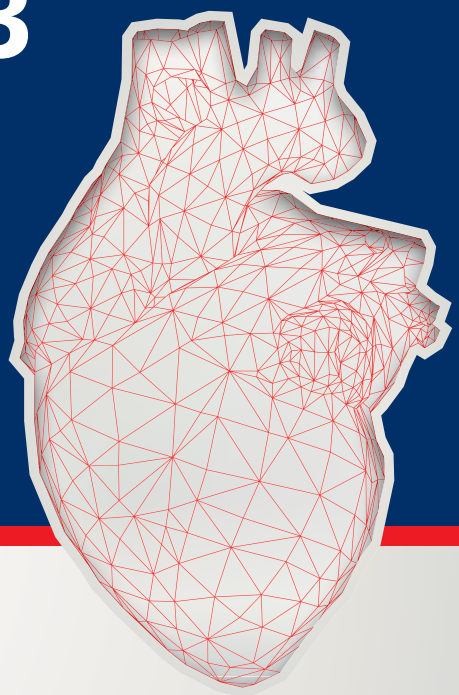

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