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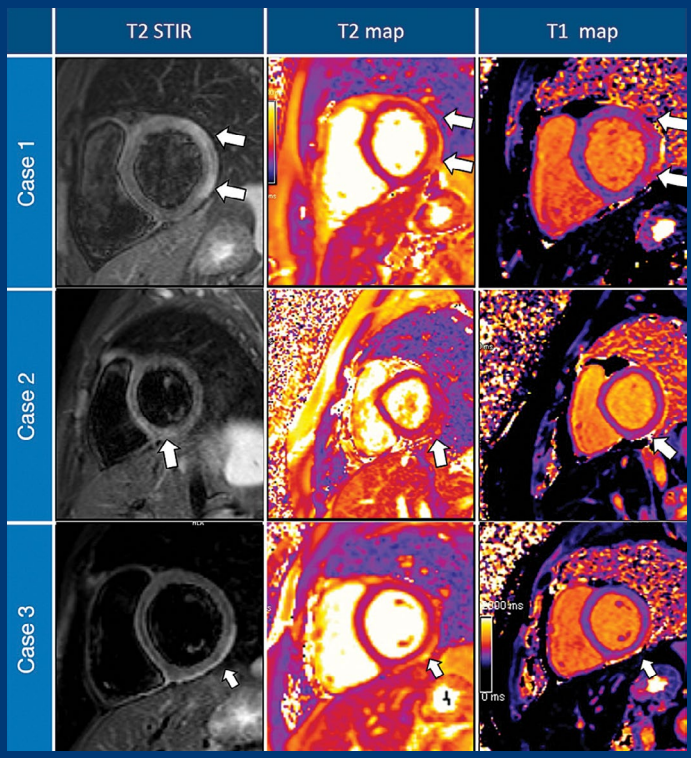

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Management of dyslipidemia in Poland: Interdisciplinary Expert Position Statement endorsed by the Polish Cardiac Society Working Group on Cardiovascular Pharmacotherapy. The Fourth Declaration of Sopot

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Introduction

Cardiovascular diseases still constitute the most frequent cause of both hospitalization and death worldwide. The classic modifiable risk factors for cardiovascular disease are malnutrition, smoking, low physical activity, increased blood pressure, prediabetes, overweight/obesity, elevated low-density lipoprotein cholesterol (LDL-C) in plasma, lowered high-density lipoprotein cholesterol (HDL-C) in plasma, and increased plasma triglycerides. However, the non-modifiable risk factors are age, sex, and early family history of ischemic heart disease or other artery diseases of atherosclerotic origin. The negative impact should also be remembered about the so-called non-classical risk factors for cardiovascular diseases, such as obstructive sleep apnea, air pollution, periodontal disease, or metabolic dysfunction — associated fatty liver disease (MAFLD). An independent risk factor for cardiovascular diseases is also an increased concentration of lipoprotein (a) — Lp(a).

The appropriate risk assessment based on both classical and non-classical risk factors is crucial when making therapeutic decisions that hence, influence the patient's prognosis.

In the first three documents [1–3], 10 conclusions were formulated to be a reference point in the debates of practicing physicians with experts during symposia/scientific conferences on the diagnosis/therapy of lipid disorder and the prevention of heart and vascular diseases. In the current document, the 11th proposal relating to lipid-lowering treatment in the era of the coronavirus disease 2019 (COVID-19) pandemic has been added.

A common problem observed in everyday practice is the erroneous misuse of the term "hypercholesterolemia" to describe any form of a lipid disorders. Use of proper nomenclature in the medical records determine not only the type of recommended therapy but also the appropriate non-drug treatment. Dyslipidemia is defined as the occurrence of abnormal plasma levels of any lipid and/or lipoprotein fraction. The term of dyslipidemia encompasses all definitions given below [4]:

— **hypercholesterolemia** — plasma LDL-C level above the recommended values in a given cardiovascular risk category (see below); primary or secondary;
— **familial hypercholesterolemia (FH)** — high plasma LDL-C level, usually correct plasma triglycerides level, monogenic (*LDLR*, *APOB*, *PCSK9* mutations) or polygenic; incidence 1 per 200–250;
— **familial combined hyperlipidemia** — elevated triglycerides and LDL-C, a mutation in the *upstream stimulatory factor 1* (*USF1*) gene; incidence 1 per 100–200;
— **hypertriglyceridemia —** plasma triglyceride level > 150 mg/dL (> 1.7 mmol/L) with normal LDL-C level;
— **severe hypertriglyceridemia** — plasma triglyceride level ≥ 500 mg/dL (≥ 5.6 mmol/L);
— **hyperlipoproteinemia (a) —** genetically determined elevated plasma Lp(a) level > 50 mg/dL; incidence 1 per 5;

Other rare genetic dyslipidemias:

— **sitosterolemia —** very high concentration of LDL-C, a mutation in the *ABCG8* and *ABCG5* genes disrupting the metabolism of phytosterols, inherited autosomal recessively; very rare incidence < 1 per 1,000,000–5,000,000;
— **familial hypoalphalipoproteinemia —** low concentration of HDL-C and correct LDL-C, a mutation in the apolipoprotein A-I (*APOA1*) gene, usually inherited autosomal dominant; incidence < 1 per million;
— **analfalipoproteinemia (Tangier disease) —** very low concentration of HDL-C or lack of this cholesterol fraction, slightly elevated triglycerides, a mutation in the *ABCA1* (*ATP-binding cassette transporter A1*, a protein that carries cholesterol esters) gene, inherited autosomal recessively; incidence of < 1 per million;
— **familial dysbetalipoproteinemia —** elevated concentration of triglycerides and total cholesterol (TC), lowered concentration of HDL-C, a mutation in the *apolipoprotein E* (*APOE*) gene, inherited autosomal dominant, incidence 1–5 per 10,000;
— **familial chylomicronemia —** triglyceride concentration often > 1000 mg/dL (11.3 mmol/L), low LDL-C concentration, the "flotation test" positive, conditioned e.g., lipoprotein lipase (LPL) deficiency or rarely mutations associated with LPL function, i.e., *APOC2, APOA5, LMF1, GPIHBP1*, inherited autosomal recessively; incidence 1–9 per million;
— **congenital lipodystrophy (Berardinelli-Seipa syndrome) —** elevated triglycerides, mutation of *AGPAT2* and *BSCL-2* (*seipin*) genes, inherited autosomal recessively; incidence 1–9 per million;
— **familial deficiency of lecithin-cholesterol acyltransferase —** low concentration of HDL-C, a mutation in *lecithin cholesterol acyltransferase* (*LCAT*) gene; incidence < 1 per million;

— **familial hypercholesterolemia inherited autosomal recessively —** high concentration of LDL-C, caused by a homozygous mutation in the LDL receptor adapter protein (*LDLRAP1*) **—** incidence < 1 per million.

In the diagnostic process, attention should be paid to possible **secondary reasons of dyslipidemia**, which may be responsible for up to 30–40% of dyslipidemia cases:

— **lifestyle —** alcohol abuse, insufficient physical activity, a high-fat diet rich in saturated fats, high carbohydrate intake;
— **diseases** — hypothyroidism (including subclinical), improperly controlled diabetes, overweight, obesity, chronic kidney disease, nephrotic syndrome, hepatic cholestasis, primary biliary cirrhosis, Cushing's syndrome, dysgammaglobulinemia, connective tissue diseases, i.e., rheumatoid arthritis and systemic lupus erythematosus;
— **pregnancy** — high values of lipid profile components relate to the physiological image of pregnancy, especially at a later stage, with normalization in the puerperium. Quantitative and qualitative changes in the lipid profile are observed. An increase in the concentration of triglycerides dominates (even by several times, but concentrations above 300 mg/dL are rarely achieved), the concentration of LDL-C may increase by up to 40%, and the concentration of HDL-C by 15–25%. These changes are adaptive, and the concentrations of individual cholesterol fractions return to pre-pregnancy values within about half a year of its termination;
— **drugs** — corticosteroids, anabolic steroids, oral progestogens and estrogens (oral contraceptives, hormone replacement therapy), selective estrogen receptor modulators (e.g., tamoxifen), retinoids, beta-blockers, thiazide diuretics (chlorthalidone), ciclosporin, mTOR kinase inhibitors (rapamycin, everolimus), cyclophosphamide, protease inhibitors used in the treatment of human immunodeficiency virus (HIV) (e.g., lopinavir, ritonavir), interferon, L-asparaginase, cyclophosphamide, atypical antipsychotics.

Familial hypercholesterolemia

In everyday clinical practice, FH remains a major challenge. Based on the molecular origin, polygenic and monogenic FH may be distinguished.

The monogenic FH is caused by the mutations in genes encoding proteins that participate in the metabolism of LDL-C particles **—** LDL receptor (85–95% of cases), rarely B-100 apolipoprotein (APOB-100) or proprotein convertase subtilisin/kexin type 9 (PCSK9). The disease is inherited autosomal dominantly. Incidence of heterozygous form 1 per 200–250 births, while homozygous 1 per 160,000–300,000 [4, 5].

The most important abnormality in heterozygous FH (HeFH) is the increased concentration of LDL-C in the blood observed from birth, usually in the range of 200–400 mg/dL. The deposition of cholesterol in tissues may lead to the formation of corneal arcus at a young age (< 45 years of age), and tendinous xanthomata (Achilles, subpatellar, and extensors of fingers of the hand). Recurrent pain in tendons, their nodules, or inflammation should therefore be a prerequisite for lipid profile control.

The risk of coronary artery disease (CAD) development in patients with definite or probable HeFH is increased by at least 10 times. It is estimated that if patients with HeFH are left untreated, premature atherosclerotic cardiovascular disease (ASCVD) occurs in about 25% of women and about 50% of men. When implemented early, long-term, and effective lipid-lowering therapy can significantly reduce this risk [4, 6, 7].

Familial hypercholesterolemia diagnosis should be considered in adults with premature CAD (women < 60 years of age and men < 55 years of age) and elevated LDL-C levels > 190 mg/dL [1]. The clinical diagnosis of FH is established on the modified Dutch Lipid Clinic Network (DLCN) criteria based on clinical data including medical history, physical examination, and lipid profile results, rarely on the basis of genetic tests confirming the presence of mutations in the previously described genes (Table 1) [8, 9].

According to the current recommendations, genetic tests may facilitate and accelerate the diagnosis but are not required for that purpose. Due to the high costs and low availability of genetic tests, it is recommended that further tests for HeFH be subjected to people with a probable or definite clinical diagnosis on the DLCN scale [1]. However, genetic tests cannot be a criterion for possible therapeutic programs or reimbursement, as they will limit the availability of novel treatment.

The most effective way to identify new cases of FH is cascade diagnostics in relatives of the identified proband based on TC or LDL-C or the presence of *LDLR*, *APOB*, or *PCSK9* mutations (if the test was performed) [10].

Approximately 20–40% of patients with a clinical diagnosis of FH fail to confirm mutations in the

Table 1. Diagnostic criteria for familial hypercholesterolemia (by: the Dutch Lipid Clinic Network scale) [8, 9].

Clinical history
Premature coronary artery disease (men < 55 years, women < 60 years) — 2 pts
Premature cerebral or peripheral vascular disease — 1 pt
Family history*
First-degree relative with premature coronary artery or vascular disease — 1 pt
First-degree relative with LDL-C level > 190 mg/dL — 1 pt
First-degree relative with tendinous xanthomata and/or corneal arcus — 2 pts
Children and adolescents aged less than 18 years with LDL-C level > 155 mg/dL — 2 pts
Physical examination
Tendon xanthomas — 6 pts
Corneal arcus below 45 years of age — 4 pts
Laboratory tests
LDL-C > 8.5 mmol/L (330 mg/dL) — 8 pts
LDL-C 6.5–8.4 mmol/L (250–329 mg/dL) — 5 pts
LDL-C 5.0–6.4 mmol/L (190–249 mg/dL) — 3 pts
LDL-C 4.0–4.9 mmol/L (155–189 mg/dL) — 1 pts
Genetic tests
Mutation in the *LDLR*, *APOB*, or *PCSK9* gene — 8 pts
DIAGNOSIS OF FAMILIAL HYPERCHOLESTEROLEMIA
Definite: > 8 pts
Probable: 6–8 pts
Possible: 3–5 pts
Unlikely: < 3 pts

*Scoring for 1 or 2 and point 3 or 4; LDL-C — low-density lipoprotein cholesterol

LDLR, *APOB*, and *PCSK9* genes. This suggests the polygenic origin of hypercholesterolemia. It has been proven that the accumulation of single nucleotide polymorphisms (SNPs), which individually slightly increase the concentration of LDL-C, may increase its concentration to values similar to those in patients with monogenic FH. The clinical picture of polygenic hypercholesterolemia is similar to that of monogenic FH, however, in the case of polygenic hypercholesterolemia, only 30% of relatives of the patient have an elevated LDL-C level. Moreover, the results of the studies indicate that the cardiovascular risk is lower in polygenic than in monogenic FH, which is probably caused by burden of LDL-C over the years. In monogenic FH, high concentration of LDL-C occurs from birth, while in polygenic FH, environmental factors have an additive effect on the concentration of LDL-C [11–13].

Theses of the Declaration

1. Dyslipidemia is the most common risk factor for cardiovascular disease in Poland. Epidemiological analyses from the WOBASZ and WOBASZ II studies indicate that in 2013–2014 (WOBASZ II study), hypercholesterolemia was present in 70.3% of men and 64.3% of women in a representative sample of adult Poles [14]. Described data are even more important due to the fact that European studies in patients with established coronary heart disease, such as the EUROASPIRE-IV study, show that the LDL-C level is elevated in more than 80% of these patients, and despite the wide use of statins, only 19.3% of patients achieve target lipid levels [15, 16].

Simultaneously, studies on the effect of cardiovascular risk factor modification over the last two decades indicate that the increase in the mean length of life in Poland has been mostly related to a reduction in mortality caused by coronary heart disease [17]. Using the IMPACT model, it was shown that a reduction in the mean cholesterol level in the Polish population that was seen in the last decades accounted for 39% of the reduction in CAD mortality [17]. These findings highlight the need for wide-ranging efforts to reduce cholesterol concentrations at the individual and population level.

2. The low detection rate of lipid disorders is one of the reasons for ineffective treatment. During the COVID-19 pandemic, a significant decrease in biochemical tests performance, including lipid profiles, was observed. It should be recalled that currently, routine lipid profile testing is recommended in all men above 40 years of age and in all women who are postmenopausal or above 50 years of age [18]. Such late testing for plasma cholesterol level, without including it in periodic health checks or occupational medicine testing panels, may reduce the opportunity for early detection of severe hypercholesterolemia. The following clinical conditions may predispose people for earlier testing, and therefore at least every adult, testing:

— established cardiovascular disease;
— established peripheral arterial disease;
— diabetes;
— obesity;
— hypertension;
— moderate or severe chronic kidney disease;
— high, very high, or extremely high cardiovascular risk;

— autoimmune inflammatory diseases (i.e., rheumatoid arthritis, systemic lupus erythematosus, or psoriasis);
— gestational diabetes;
— hypertension in pregnancy;
— clinical manifestations of dyslipidemia (such as tendon xanthomas, xanthelasma, or corneal lipid degeneration [corneal arcus]);
— family history of lipid disorders or premature cardiovascular disease;
— antiretroviral treatment.

In all cases, testing should include direct TC and triglyceride level measurements and calculation of LDL-C (using the Friedewald formula) and non-HDL cholesterol (non-HDL-C) levels. In case of hypertriglyceridemia (> 400 mg/dL [> 4.5 mmol/L]), direct LDL-C level measurement is necessary. It is not justified to measure single lipid fractions without evaluation of the full lipid profile, and additional measurements of apolipoprotein B (apoB), apolipoprotein A (apoA), Lp(a) levels and determinations of the apoB to apoA ratio and the non-HDL-C to HDL-C ratio may be considered in selected clinical settings. Traditionally, lipid levels are measured in fasting conditions but studies indicate that measurements of most lipid parameters yield similar values in postprandial and fasting conditions. The exception is triglyceride level which shows a postprandial increase by about 30 mg/dL (0.3 mmol/L) [19].

Determination of Lp(a) concentration is recommended in selected subjects at high cardiovascular risk or in order to clarify the classification in the European guidelines (point 7 of the Declaration). According to the current recommendation of European experts, the determination of Lp(a) concentration may be considered at least once in a lifetime in every adult [4].

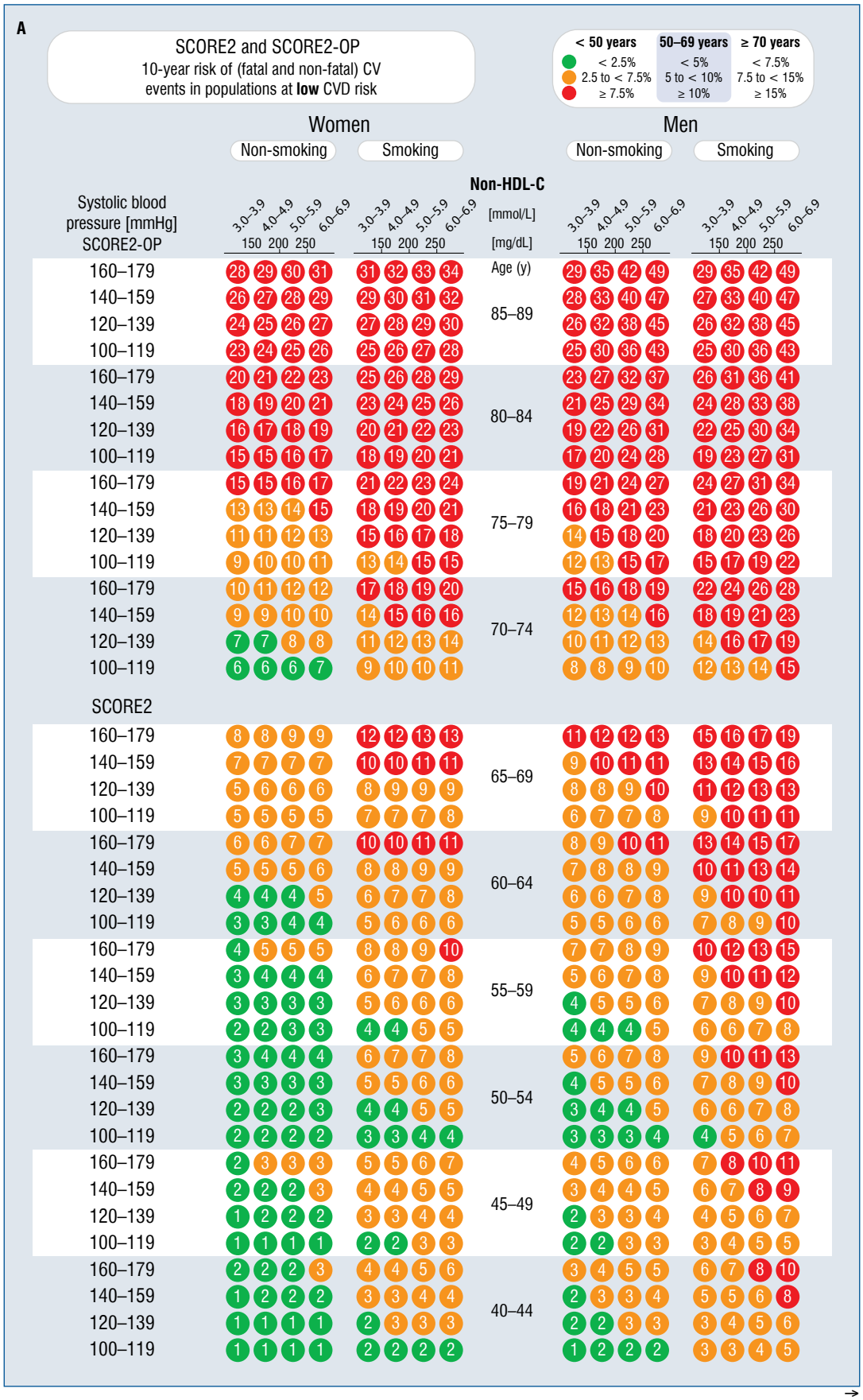
Following initiation of lipid-lowering therapy, lipid profile should be evaluated every 8 ± 4 weeks to adjust therapy until target lipid levels are achieved. In patients with adequate on-treatment lipid levels, annual lipid profile testing is recommended. In addition, creatine kinase (CK) and alanine aminotransferase (ALT) levels should be evaluated prior to the initiation of lipid-lowering therapy. Single ALT level retesting is indicated at 8–12 weeks after lipid-lowering therapy initiation or dose escalation. Further routine CK and ALT level retesting are not necessary unless prompted by clinical symptoms [20].

3. The individual goal of lipid-lowering therapy depends on the cardiovascular risk. In order to plan lipid-lowering treatment, it is important to comprehensively assess the patient's health condition, taking into account the presence of classical and non-classical cardiovascular risk factors. According to the previous recommendations on the prevention of cardiovascular diseases, a risk assessment should be based on the SCORE scale in modification proposed for the Polish population [21]. Recently, a new SCORE2 risk assessment scale based on non-HDL-C has been proposed in the "European Heart Journal". Contrary to SCORE, it is not calibrated for data from Poland, however, it is possible to use the calculation of the category of high-risk countries for Polish patients. The SCORE2 and SCORE2-OP scales have been introduced as currently applicable to the new guidelines of the European Society of Cardiology 2021 on the prevention of heart and vascular diseases 2021. The document includes 4 forms that differ in the baseline cardiovascular risk (Fig. 1A–D) [22]. Also proposed herein, cardiovascular risk categories modified on the basis of the new guidelines, which are presented in Table 2 [22].

Besides the low, moderate, high, and very high cardiovascular risk categories, the extremely high risk group has remained to be defined as a condition after multiple cardiovascular events and/or revascularizations, percutaneous left main stem stenting or/and multivessel CAD (comprehensive angioplasty in multivessel coronary disease), generalized atherosclerosis — multiple vascular beds with additional risk factors or the progression of atherosclerotic cardiovascular disease in patients who achieved and consistently maintained LDL-C < 55 mg/dL (< 1.4 mmol/L).

After cardiovascular risk assessment, intervention should be planned appropriately. The primary therapeutic goal is to achieve the target LDL-C concentration based on the patient's cardiovascular risk. The results of the latest studies indicate that a very significant reduction of LDL-C is associated with an improved prognosis of patients, a reduction in the risk of cardiovascular events, and a reduction in the severity of atherosclerotic changes in blood vessels [22, 23]. After achieving the target LDL-C concentration, a secondary goal is to achieve the target non-HDL-C concentration. The results of previous studies have revealed that both in the group of women and in the group of men there is a significant increase in the risk of cardiovascular events along with the increase in the concentration of non-HDL-C (Fig. 2) [25].

After achieving the target levels of LDL-C and non-HDL-C a practicing physician may set additional goals (e.g., triglyceride levels) (Table 3).


A
SCORE2 and SCORE2-OP
10-year risk of (fatal and non-fatal) CV events in populations at low CVD risk
< 50 years
< 2.5%
2.5 to < 7.5%
≥ 7.5%
50–69 years
< 5%
5 to < 10%
≥ 10%
≥ 70 years
< 7.5%
7.5 to < 15%
≥ 15%
Women
Non-smoking
Smoking
Men
Non-smoking
Smoking
Non-HDL-C
[mmol/L]
[mg/dL]
3.0–3.9
4.0–4.9
5.0–5.9
6.0–6.9
150 200 250
Systolic blood pressure [mmHg]
SCORE2-OP
SCORE2
Age (y)
160–179 28 29 30 31 31 32 33 34 29 35 42 49 29 35 42 49
140–159 26 27 28 29 29 30 31 32 28 33 40 47 27 33 40 47
120–139 24 25 26 27 27 28 29 30 26 32 38 45 26 32 38 45
100–119 23 24 25 26 25 26 27 28 25 30 36 43 25 30 36 43
85–89
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140–159 18 19 20 21 23 24 25 26 21 25 29 34 24 28 33 38
120–139 16 17 18 19 20 21 22 23 19 22 26 31 22 25 30 34
100–119 15 15 16 17 18 19 20 21 17 20 24 28 19 23 27 31
80–84
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75–79
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160–179 8 8 9 9 12 12 13 13 11 12 12 13 15 16 17 19
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100–119 5 5 5 5 7 7 7 8 6 7 7 8 9 10 11 11
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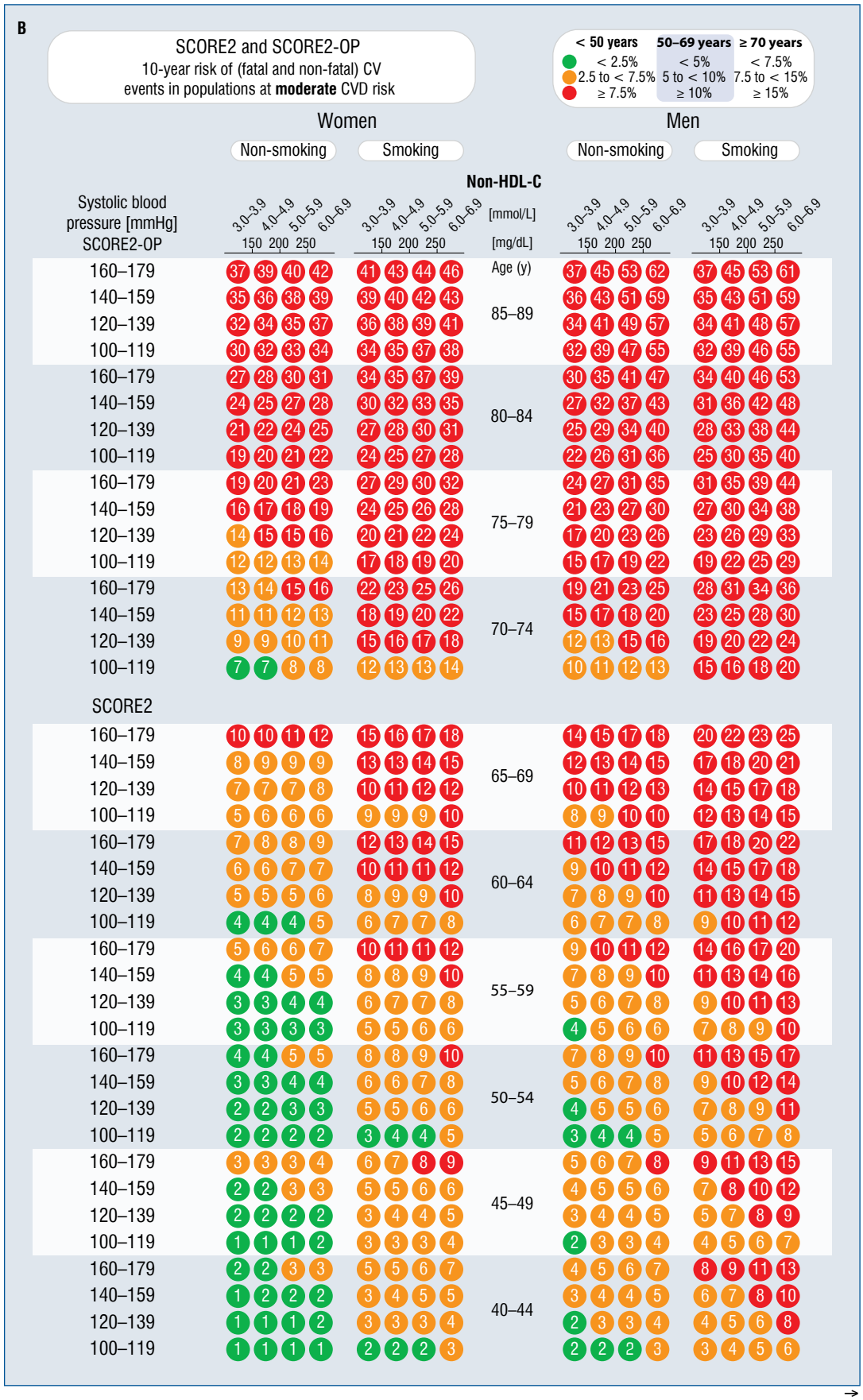
B
SCORE2 and SCORE2-OP
10-year risk of (fatal and non-fatal) CV events in populations at **moderate** CVD risk
< 50 years
50–69 years
≥ 70 years
< 2.5%
2.5 to < 7.5%
≥ 7.5%
< 5%
5 to < 10%
≥ 10%
< 7.5%
7.5 to < 15%
≥ 15%
Women
Men
Non-smoking
Smoking
Non-HDL-C
Systolic blood pressure [mmHg]
SCORE2-OP
SCORE2
3.0–3.9
4.0–4.9
5.0–5.9
6.0–6.9
[mmol/L]
150 200 250
[mg/dL]
Age (y)
160–179 37 39 40 42 41 43 44 46 37 45 53 62 37 45 53 61
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140–159 11 11 12 13 18 19 20 22 15 17 18 20 23 25 28 30
120–139 9 9 10 11 15 16 17 18 12 13 15 16 19 20 22 24
100–119 7 7 8 8 12 13 13 14 10 11 12 13 15 16 18 20
70–74
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120–139 7 7 7 8 10 11 12 12 10 11 12 13 14 15 17 18
100–119 5 6 6 6 9 9 9 10 8 9 10 10 12 13 14 15
65–69
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45–49
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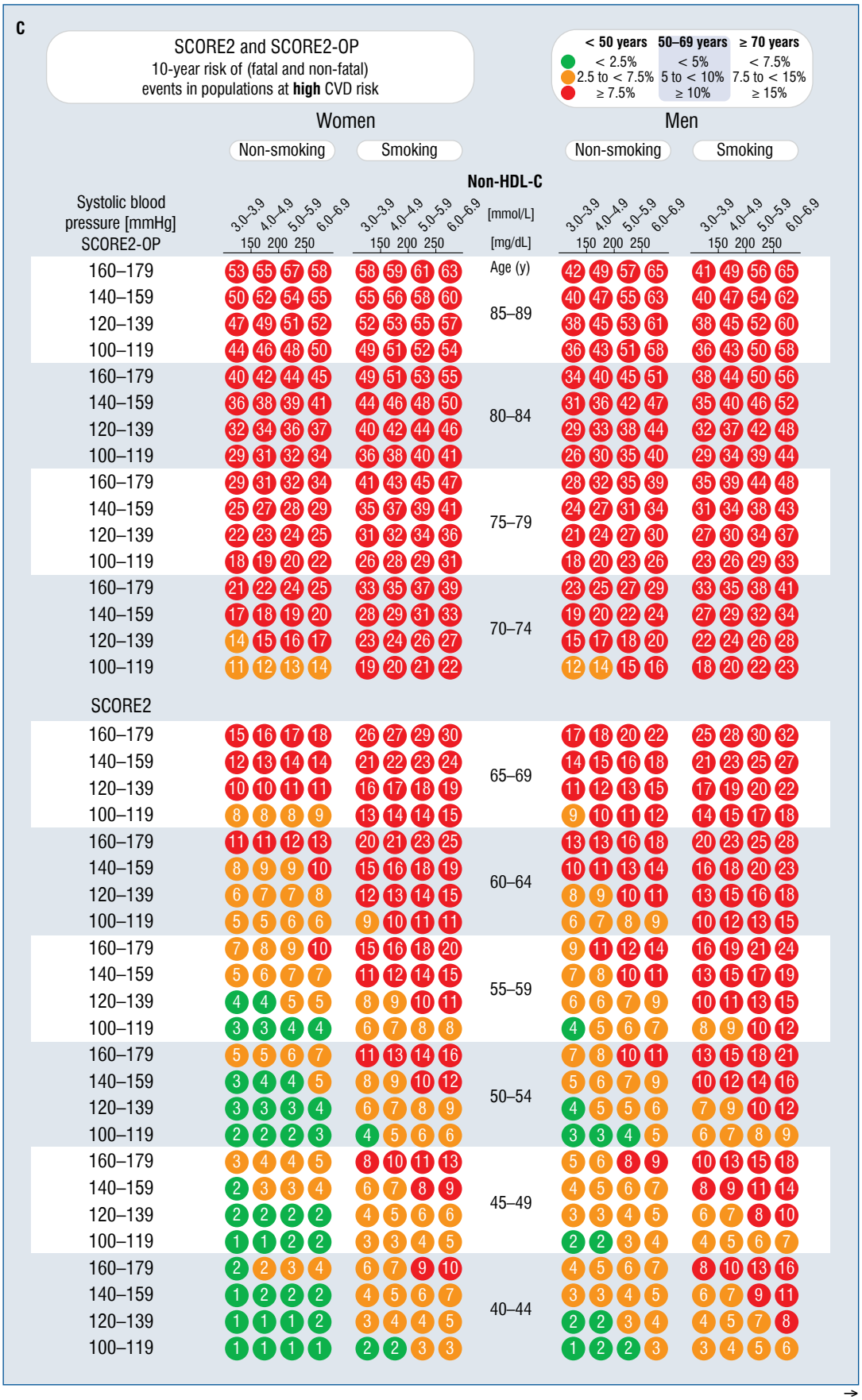
40–44


C
SCORE2 and SCORE2-OP
10-year risk of (fatal and non-fatal) events in populations at high CVD risk
< 50 years
50–69 years
≥ 70 years
< 2.5%
< 5%
< 7.5%
2.5 to < 7.5%
5 to < 10%
7.5 to < 15%
≥ 7.5%
≥ 10%
≥ 15%
Women
Men
Non-smoking
Smoking
Non-HDL-C
Systolic blood pressure [mmHg]
SCORE2-OP
SCORE2
3,0–3,9
4,0–4,9
5,0–5,9
6,0–6,9
150 200 250
[mmol/L]
[mg/dL]
Age (y)
160–179 53 55 57 58 58 59 61 63 42 49 57 65 41 49 56 65
140–159 50 52 54 55 55 56 58 60 40 47 55 63 40 47 54 62
120–139 47 49 51 52 52 53 55 57 38 45 53 61 38 45 52 60
100–119 44 46 48 50 49 51 52 54 36 43 51 58 36 43 50 58
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160–179 40 42 44 45 49 51 53 55 34 40 45 51 38 44 50 56
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140–159 1 2 2 2 4 5 6 7 3 3 4 5 6 7 9 11
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100–119 1 1 1 1 2 2 3 3 1 2 2 3 3 4 5 6
40–44

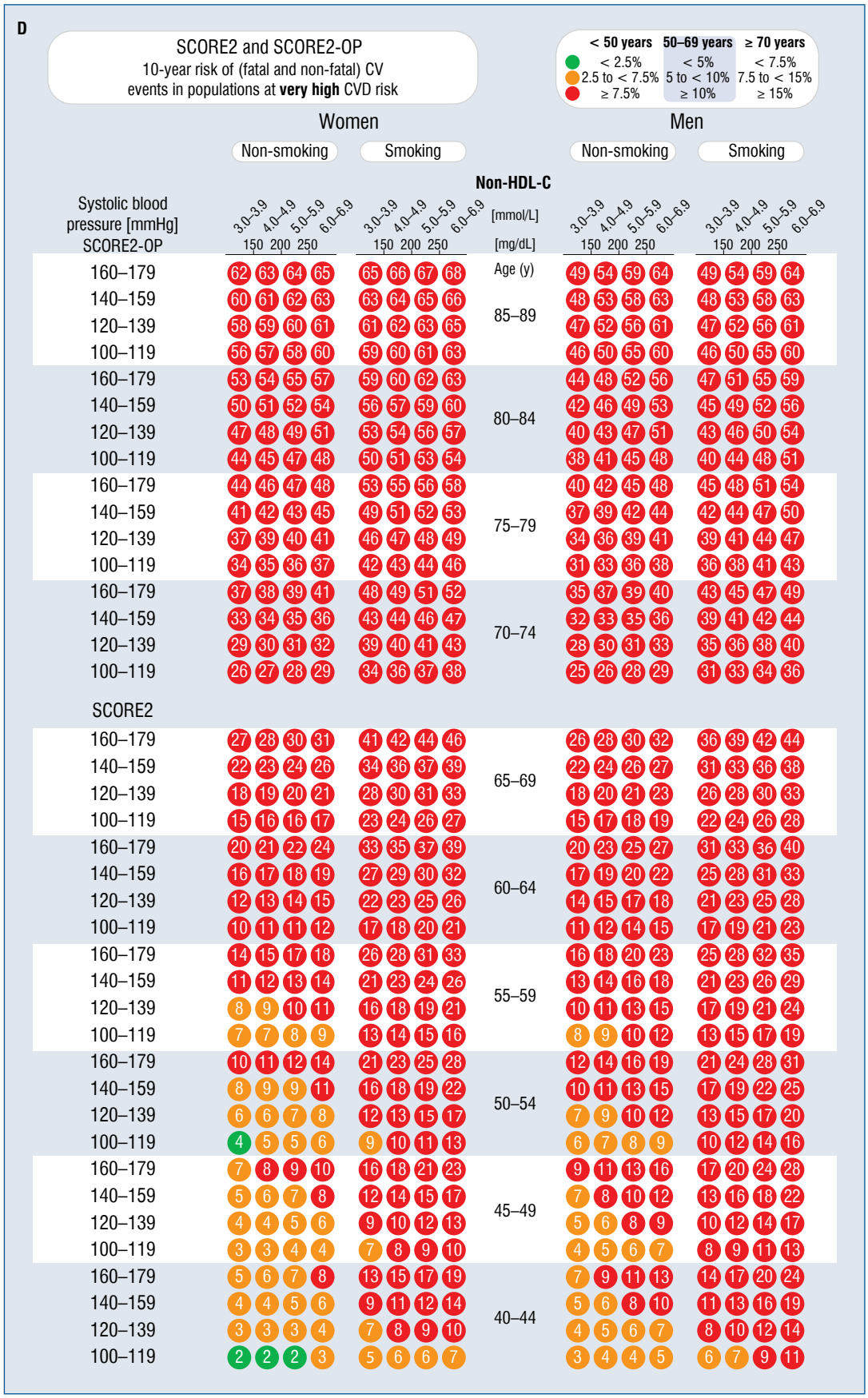

Figure 1. SCORE2 and SCORE2-OP risk assessment scale; **A.** Low risk; **B.** Moderate risk; **C.** High risk; **D.** Very high risk (source: [22]); SCORE — Systematic Coronary Risk Estimation; CV — cardiovascular; CVD — cardiovascular disease; non-HDL-C — non-high-density lipoprotein cholesterol.

Table 2. Cardiovascular risk categories according to the latest guidelines of the European Society of Cardiology 2021 on the prevention of cardiovascular diseases (CVD) (source: [22]).

Patient category	Subgroups	Risk categories	CVD risk and therapy benefit estimation
Apparently healthy persons			
Persons without established ASCVD, DM, CKD, familial hypercholesterolemia	< 50 years	Low- to high-risk	10-year CVD risk estimation (SCORE2). Lifetime risk and benefit estimation (e.g., with the LIFE-CVD lifetime model) to facilitate the communication of CVD risk and treatment benefits
	50–69 years	Low- to very high-risk	10-year CVD risk estimation (SCORE2). Lifetime benefit estimation of risk factor treatment (e.g., with the LIFE-CVD lifetime model) to facilitate the communication of treatment benefits
	≥ 70 years	Low- to very high-risk	10-year CVD risk estimation (SCORE2-OP). Lifetime benefit estimation of risk factor treatment (e.g., with the LIFE-CVD lifetime model) to facilitate the communication of treatment benefits
Patients with CKD			
CKD without diabetes or ASCVD	Moderate CKD (eGFR 30–44 mL/min/1.73 m^2 and ACR < 30 **or** eGFR 45–59 mL/min/1.73 m^2 and ACR 30–300 **or** eGFR ≥ 60 mL/min/1.73 m^2 and ACR > 300)	High-risk	N/A
	Severe CKD (eGFR < 30 mL/min/1.73 m^2 **or** eGFR 30–44 mL/min/1.73 m^2 and ACR > 30)	Very high-risk	N/A
Familial hypercholesterolemia			
Associated with markedly elevated cholesterol levels	N/A	High-risk	N/A
Patients with type 2 diabetes mellitus			
Patients with type 1 DM above according to these criteria	Patients with well controlled short-standing DM (e.g., < 10 years), no evidence of TOD and no additional ASCVD risk factors	Moderate- risk	N/A
	Patients with DM without ASCVD and/or severe TOD, and not fulfilling the moderate risk criteria	High-risk	Residual 10-year CVD risk estimation after general prevention goals (e.g., with the ADVANCE risk score or DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g., DIAL model)
	Patients with DM with established ASCVD and/or severe TOD: • eGFR < 45 mL/min/1.73 m^2 irrespective of albuminuria • eGFR 45–59 mL/min/1.73 m^2 and microalbuminuria (ACR 30–300 mg/g) • proteinuria (ACR > 300 mg/g) • presence of microvascular disease in at least 3 different sites (e.g., microalbuminuria plus retinopathy plus neuropathy)	Very high-risk	Residual 10-year CVD risk estimation after general prevention goals (e.g., with the SMART risk score for established CVD or with the ADVANCE risk score or with the DIAL model). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g., DIAL model)

→

Table 2 (cont.). Cardiovascular risk categories according to the latest guidelines of the European Society of Cardiology 2021 on the prevention of cardiovascular diseases (CVD) (source: [22]).

Patient category	Subgroups	Risk categories	CVD risk and therapy benefit estimation
Patients with established ASCVD			
Documented ASCVD, clinical or unequivocal on imaging. Documented clinical ASCVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented ASCVD on imaging includes plaque on coronary angiography or carotid ultrasound or on CTA. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery	N/A	**Very high-risk**	Residual CVD risk estimation after general prevention goals (e.g., 10-year risk with the SMART risk score for patients with established CVD or 1- or 2-year risk with EUROASPIRE risk score for patients with CHD). Consider lifetime CVD risk and benefit estimation of risk factor treatment (e.g., SMART-REACH model; or DIAL model if diabetes)

ACR — albumin-to-creatinine ratio (to convert mg/g to mg/mmol: divide by 10); ACS — acute coronary syndrome; ADVANCE — Action in Diabetes and Vascular disease: preterAx and diamicroN-MR Controlled Evaluation; AMI — acute myocardial infarction; ASCVD — atherosclerotic cardiovascular disease; CHD — coronary heart disease; CKD — chronic kidney disease; CTA — computed tomography angiography; DIAL — Diabetes lifetime-perspective prediction; DM — diabetes mellitus; eGFR — estimated glomerular filtration rate; IMT — intima–media thickness; LIFE-CVD — LIFEtime-perspective CardioVascular Disease; N/A — not applicable; PAD — peripheral artery disease; REACH — Reduction of Atherothrombosis for Continued Health; SCORE — Systematic Coronary Risk Estimation; SMART — Secondary Manifestations of Arterial Disease; TIA — transient ischemic attack; TOD — target organ damage

This document maintains the category of "extremely high cardiovascular risk", which is based on the Third Sopot Declaration and guidelines of the American endocrine societies (Tables 2 and 3) [23].

4. It is necessary to introduce standardised laboratory report forms. The expert consensus panel suggests a recommendation to standardize laboratory report forms so as they indicate target ranges in accordance with the most recent recommendations and medical knowledge and do not generate a risk of potential errors by patients or physicians. A proposal of such a form is shown in Figure 3.

It is not necessary to measure the fasting lipid profile. The only exception is **triglycerides**, which still absolutely must be measured in fasting conditions. Even in people with normal triglyceride levels (up to 150–179 mg/dL fasting), however, there may exist a status of lipid intolerance, common in patients with diabetes, are obese, or who are overweight. For these patients, the currently standardized fat tolerance test for postprandial lipemia is recommended. It is performed in people with normal fasting triglycerides, after refraining from a meal for 10–12 hours and measuring triglycerides again 4 hours after administration of a standardized fatty meal (Lipid Test Control®). Triglyceride values > 220 mg/dL allow diagnoses of abnormal postprandial lipemia. Other lipid-lowering drugs, apart from those listed in this chapter, including over-the-counter drugs, are not relevant in the lipid-lowering pharmacotherapy of patients at very high and extremely high cardiovascular risk.

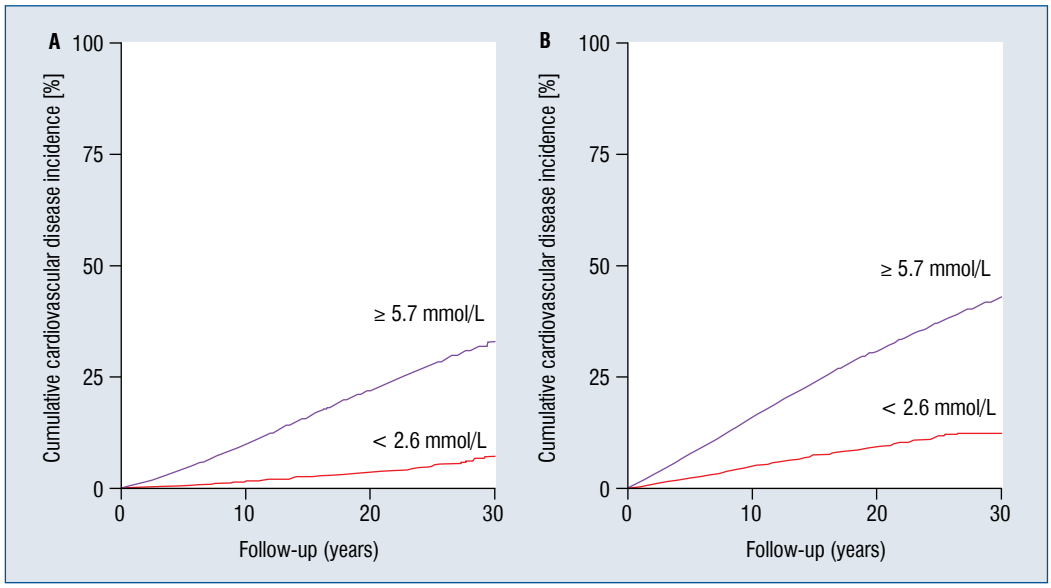

Figure 2. The risk of cardiovascular events depending on the non-high-density lipoprotein cholesterol (non-HDL-C) levels; **A.** Women; **B.** Men; p < 0.0001 (adapted from: [25], modified).

Table 3. Target concentration of low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (non-HDL-C) and triglycerides (TG) depending on the cardiovascular risk profile (own work).

Risk category	Primary goal — LDL-C	Secondary goal — non-HDL-C	Additional goal — TG
EXTREMELY HIGH	< 35 mg/dL (< 0.9 mmol/L)	< 65 mg/dL (< 1.7 mmol/L)	< 150 mg/dL (< 1.7 mmol/L)
VERY HIGH	< 55 mg/dL (< 1.4 mmol/L)	< 85 mg/dL (< 2.2 mmol/L)	< 150 mg/dL (< 1.7 mmol/L)
HIGH	< 70 mg/dL (< 1.8 mmol/L)	< 100 mg/dL (< 2.6 mmol/L)	< 150 mg/dL (< 1.7 mmol/L)
MODERATE	< 100 mg/dL (< 2.6 mmol/L)	< 130 mg/dL (< 3.4 mmol/L)	< 150 mg/dL (< 1.7 mmol/L)
LOW	< 115 mg/dL (< 3.0 mmol/L)	< 145 mg/dL (< 3.8 mmol/L)	< 150 mg/dL (< 1.7 mmol/L)

5. It is necessary to recommend lifestyle modifications in all patients. Non-drug treatment is the basis of therapy and translates into a reduction of cardiovascular risk, improvement of the patients' prognosis and functioning. When considering groups of patients with any atherosclerotic diseases, non-drug treatment consists of lifestyle modification in a broad sense. A change in nutrition is the basic approach that allows reducing LDL-C levels. However, a healthy diet does not only reduce lipid levels but also has a beneficial effect on other cardiovascular risk factors beyond the LDL-C level. Nutrition has a role mostly in the prevention and treatment of mild and moderate hypercholesterolemia in primary prevention, and of atherogenic dyslipidemia, particularly by its effect on triglycerides, small dense LDL-C, and low HDL-C levels which are associated with obesity and insulin resistance. An example of the food products' impact on the reduction of LDL-C is presented in Table 4 [26].

The major components of the dietary approach in subjects with lipid disorders include reduction of total fat intake to 25–35% of the overall energy intake, saturated fat intake to 7% of the overall energy intake, and cholesterol intake to < 200 mg daily [16–21, 23, 24, 27, 28]. In particular, saturated fatty acids are a nutritional factor that has the strongest effect on LDL-C level. It has been estimated that per each additional 1% of energy intake from saturated fat, serum LDL-C level increases by 0.8–1.6 mg/dL [17–21, 23, 24, 27, 28]. Dietary treatment of hypertriglyceridemia should include reduction of alcohol, carbohydrate intake, in particular intake of simple sugars, and weight loss should be recommended in obese subjects.

LIPID PROFILE

Date:..... Test no:..... Ordering physician:..... Laboratory remarks:.....

PATIENT NAME: .....

PESEL identification number:.....

LIPID FRACTIONS	RESULT	TARGET VALUE
Total cholesterol [mg/dL]	…	< 190
LDL-C [mg/dL]	…	Target values based on the cardiovascular risk
HDL-C [mg/dL]	…	> 40 (men)
		> 48 (women)
Triglycerides [mg/dL]	…	< 150
Non-HDL-C [mg/dL]	…	
OPTIONAL LIPIDOGRAM FRACTIONS		
Lipoprotein (a)	…	
Apolipoprotein B	…	

NOTE: The primary therapeutic goal is LDL-C concentration; target value for subjects at extremely high, very high, high, moderate or low risk is < 35 mg/dL, < 55 mg/dL, < 70 mg/dL, < 100 mg/dL, and < 115 mg/dL, respectively, and in some subjects, it may be defined by a physician as an INDIVIDUAL TREATMENT GOAL.

NOTE: The secondary therapeutic goal is non-HDL-C concentration; target value for subjects at extremely high, very high, high, moderate or low risk is < 65 mg/dL, < 85 mg/dL, < 100 mg/dL, < 130 mg/dL, and < 145 mg/dL, respectively.

NOTE: LDL-C level ≥ 190 mg/dL (≥ 5.0 mmol/L) in adults and ≥ 160 mg/dL (≥ 4.1 mmol/L) in subjects below 18 years of age may indicate familial hypercholesterolemia.

NOTE: The above lipid profile testing results should be consulted with the referring physician

REFERRING PHYSICIAN: Target LDL-C level has been set at: < .....

.....

Physician signature and stamp

Figure 3. A proposed appropriate form to report lipid profile testing results; LDL-C — low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; non-HDL-C — non-high-density lipoprotein cholesterol.

In severe hypertriglyceridemia, intake of all fat should be significantly reduced due to the presence of chylomicrons.

An important adjunct to lifestyle modifications (appropriate dietary treatment and adequate physical activity) may be the use of a product based on plant substances with lipid-lowering effects supported by evidence-based medicine (EBM) data. These currently include preparations containing monacolin K and bergamots products. Monacolin, a constituent of red yeast rice is natural lovastatin, which may reduce LDL-C level by 20%. Bergamot is a type of orange from Calabria. The extract of this fruit has a beneficial effect on lipid profile and carbohydrate metabolism. Another example of non-drug treatment relates to proper sleep hygiene (6–8 hours/day/adult), reducing exposure to air pollution, and quitting smoking. It should be remembered that in addition to smoking cessation recommendations, pharmacological interventions (cytisine, nicotine replacement therapy, bupropion, varenicline), some kind of alternative in the treatment of smoking patients who continue to smoke despite the aforementioned interventions, can be offered as alternative harm reduction products which heat tobacco instead of burning it (heat-not-burn, e.g., IQOS — approved, for example, by the American Food and Drug Administration) [29].

Table 4. The impact of food products on the reduction of low-density lipoprotein cholesterol (LDL-C) (adapted from: [26], modified)

Food	Effect on LDL-C
Foods high in n-6 PUFA and/or MUFA and low in SFA; e.g., canola oil	Moderate to large reduction
Foods high in soluble fiber; e.g., psyllium, oats, and barley	Moderate reduction
Foods with added plant sterols or stanols	Moderate reduction
Flaxseeds (whole)	Small to moderate reduction
Soy protein	Small to moderate reduction
Tomatoes	Small to moderate reduction
Almonds	Small reduction
Fish	No clear effect
Decaffeinated coffee (in place of regular coffee)	No effect
Filtered coffee	No effect
Foods high in SFA or trans fatty acids (i.e., solid and tropical fats)	Moderate to large increase
Unfiltered coffee (in place of filtered coffee)	Moderate to large increase
Avocados	Moderate to large reduction
Turmeric	Moderate to large reduction
Hazelnuts	Small to moderate reduction
Pulses	Small to moderate reduction
Green tea	At least small reduction
Fiber, whole grains	Small reduction
Walnuts	Small reduction
Darker roast coffee	No clear effect
Fructose (in place of sucrose/glucose)	No clear effect
Marine oils (high in long-chain n-3 PUFA)	Very small increase
Free sugars	Small increase
Coffee (in place of tea)	Small to moderate increase
Garlic powder	Small to moderate reduction
Probiotics and prebiotics	Small to moderate reduction
Cumin	Small to moderate reduction
Ginger	Small reduction
Eggs	Small increase
Foods high in resistant starch	Small reduction
High-polyphenol olive oil (in place of low-polyphenol)	Small reduction
Foods high in α-linolenic acid, e.g., flaxseed oil	No clear effect
Foods high in medium-chain (in place on of long-chain) SFA	No clear effect
Grapefruits	No effect
Berries	Small to moderate reduction
Garlic	Small to moderate reduction
Black tea	At least small reduction
Dark chocolate/cocoa products	At least small reduction
Alcoholic drinks	Small reduction
Dairy products (all, high-fat, low-fat)	No clear effect
Grape polyphenols	No clear effect
Synbiotics	No clear effect
Whey protein	No clear effect
Fruit juice	No effect
Red meat	No effect
Sweeteners	No effect

MUFA — monounsaturated fatty acids; PUFA — polyunsaturated fatty acids; SFA — saturated fatty acids

6. Statins are the basis of lipid-lowering pharmacotherapy. In accordance with the wording of previous Declarations of Sopot [1–3], we continue to endorse and highlight the recommendation for statins as the major drugs used to treat hypercholesterolemia. They account for more than 90% of all lipid-lowering drugs prescribed in Poland, and their use has been increasing year by year. Statins reduce hepatic cholesterol synthesis by competitive inhibition of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase. They are among the best studied drugs used for cardiovascular disease prevention, and their beneficial effect on cardiovascular mortality has been shown in multiple clinical trials. Of HMG-CoA reductase inhibitors used in Poland, rosuvastatin and atorvastatin have the most effective lipid-lowering effect.

The smallest recommended rosuvastatin dose, 5–10 mg, is equivalent to 20–30 mg of atorvastatin. It means that the conversion of the lipid-lowering efficacy of rosuvastatin to atorvastatin corresponds more to a ratio of 1:3 than 1:2. Thus, the availability of 15 mg and 30 mg rosuvastatin doses increases the ability to switch statin therapy to this drug in those patients who were previously treated with 40 mg and 80 mg of atorvastatin, respectively. These intermediate statin doses allow more effective attainment of target LDL-C levels by individualizing the therapy. An increase has been recently seen in the intensifying of lipid-lowering therapy by prescriptions of intermediate statin doses by practitioners. Atorvastatin undergoes hepatic biotransformation by the cytochrome 450 (CYP) 3A4 isoform, while rosuvastatin is metabolized in the liver to a much lesser degree, interacting with CYP2C9. These differences are important due to potential drug interactions which are very rare with rosuvastatin. Rosuvastatin is contraindicated in patients with severe renal failure and glomerular filtration rate (GFR) below 30 mL/min/1.73 m^2. A mnemonic distinction "atorvastatin safer in a patient with kidney disease" and "rosuvastatin safer in a patient with liver disease" is still popular and may be helpful in choosing a specific molecule (results from the PLANET I and PLANET II studies still await publication). However, it would not be reasonable, by oversimplifying this rule in practice, to refrain from the use of the most effective lipid-lowering drug available on the market (rosuvastatin) in those patients in whom renal function allows it (i.e., with the estimated GFR > 30 mL/min) [30, 31]. The need to use a statin in kidney and heart transplant patients should not be forgotten. Many of the standard immunosuppressive drugs increase or cause lipid disorders. Some, such as cyclosporine and tacrolimus, may increase the levels of concomitant statins. Thus, it is necessary to be vigilant in terms of possible adverse effects and to individualize the dosing schedule of lipid-lowering drugs.

The major goal of the treatment of dyslipidemia is to lower LDL-C level. As indicated by the new recommendations in the present document, treatment goals are currently very rigorous and only the use of potent drugs in high doses may help achieve or approach these goals. If the goal is not achieved, the dose should be increased or statin should be switched to a more effective treatment in reducing LDL-C. Regarding atorvastatin and rosuvastatin, their use in maximal doses was shown to induce regression of atherosclerotic lesions in diseased coronary vessels (ASTEROID and SATURN studies) [32, 33].

In 2021, another statin will be available in Poland — pitavastatin. Pitavastatin lowers LDL-C > 50%, placing it in the group of high-intensity statins, in addition to atorvastatin and rosuvastatin. It is also worth underling its negligible effect on glycemia and the low risk of drug interactions. Pitavastatin is contraindicated only in patients being treated with cyclosporine and lopinavir/ritonavir. Caution is advised in combination therapy with fibrates. The objection to pitavastatin is noted in a relatively small number of randomized clinical trials, limited primarily to people of the Asian race.

Familial hypercholesterolemia requires intensive lipid-lowering treatment, regardless of the genetic test result. The therapeutic goal in subjects with FH depends on the assessment of cardiovascular risk. Patients with FH with ASCVD or other major risk factors are in a very high-risk group and the goal is to reduce LDL-C ≥ 50% and below 55 mg/dL. Subjects with FH but without the aforementioned factors are in the high-risk category with the goal of reducing LDL-C ≥ 50% and below 70 mg/dL [4].

The first-line drugs are effective statins (rosuvastatin and atorvastatin), the next step is combined therapy with ezetimibe [4, 34]. In the case of FH patients with a very high risk who do not achieve the treatment goal on the maximally tolerated combined therapy with a potent statin and ezetimibe, and in those with statin intolerance, PCSK9 inhibitors should be included, this is reimbursed in Poland under drug programs. In terms of newer therapies, high efficacy has also been demonstrated for inclisiran, administered by injection once every 6 months, belonging to

the small interfering ribonucleic acid (siRNA) type and bempedia acid acting on the ATP-citrate lyase. Moreover, evinacumab, a human monoclonal antibody inhibiting angiopoietin-like proteins 3 (ANGPTL3), with a specific potential role in the coexistence of hypercholesterolemia with hypertriglyceridemia is a new direction [4, 35, 36]. There are lipid-lowering drugs with separate mechanisms, which are unavailable in Poland, and are dedicated to homozygous, severe family hypercholesterolemia (e.g., mipomersen).

It should be underlined that the primary goal of treating patients with FH is to prevent cardiovascular events through early diagnosis and effective treatment.

7. Elevated lipoprotein (a) concentration is associated with an increased cardiovascular risk. Lipoprotein (a) is a particle similar to LDL, however, unlike it, it additionally contains apolipoprotein (a), which is evolutionarily derived from plasminogen and may influence the fibrinolysis process. Increased Lp(a) levels are associated with an increased number of cardiovascular events, independent of LDL-C levels and other risk factors. It is estimated that 1 in 5 people have a concentration of Lp(a) > 50 mg/dL, and a very high concentration of Lp(a) > 180 mg/dL even 1 in 100 people [36, 37]. The *LPA* locus on chromosome 6 (6q26–27) is one of the strongest determinants of CAD. It has been revealed that the relationship between *LPA* gene variants and cardiovascular events was maintained in people with LDL-C ≤ 70 mg/dL on statin therapy [38].

Determination of Lp(a) concentration should be considered in every adult once in a lifetime to early identify patients with very high Lp(a) levels > 180 mg/dL and cardiovascular risk comparable to those with HeFH [4]. However, the determination of Lp(a) should be performed in particular in patients with:

— a burdening family history of premature ASCVD;
— a moderate to high cardiovascular risk;
— premature ASCVD or recurrent despite optimal LDL-C control;
— family history of high Lp(a) > 90 mg/dL in a first-degree relative [39].

Cardiovascular risk related to Lp(a) concentration can be estimated as low, moderate, high, and very high based on its ranges (Table 5) [40].

Lifestyle modification, including diet and physical activity, have minimal effect on Lp(a) concentration. Currently, commercially available drugs reduce Lp(a) levels to an unsatisfactory degree, and lipoprotein apheresis is effective among the therapies available in Poland (Table 6). Particularly ineffective in the fight against elevated levels of Lp(a) are statins. Previous analyzes indicate that a 100 mg/dL reduction in Lp(a) should translate into a long-term 45% reduction in cardiovascular risk. Currently, in phase 3 of clinical trials, there are new drugs targeting apolipoprotein (a) (antisense oligonucleotide and siRNA), which may reduce Lp(a) concentration by up to 90% (pelacarsen, olpasiran) [40–45].

Table 5. Cardiovascular risk related to lipoprotein (a) concentration.

Lipoprotein (a)		Effect on cardiovascular risk
[mg/dL]	[nmol/L]	
18–40	32–90	Low
40–90	90–200	Moderate
90–180	200–400	High
> 180	> 400	Very high

Table 6. Examples of therapies lowering lipoprotein (a).

Therapy	Reduction of lipoprotein (a) concentration	Effect on the reduction of cardiovascular events
Niacin	19–39%	No reduction of cardiovascular events
PCSK inhibitors	20–30%	Sub-analyzes from clinical trials indicate a reduction in cardiovascular events in patients with lipoprotein (a) > 100 mg/dL
Lipoprotein apheresis	70–75%	Long-term therapy reduces the annual rate of major adverse cardiovascular events by 80–85%

PCSK9 — proprotein convertase subtilisin/kexin type 9

8. Statin tolerance is the rule with few exceptions. All statins, including the most effective ones — atorvastatin and rosuvastatin, are very well tolerated by patients, and the incidence of specific adverse effects is rare. However, the statin group is burdened with a strong nocebo effect, and the frequency of reported adverse effects is not increased with blinded drug administration compared to placebo, which has been proven in the recent SAMSON study.

However, patients should be informed about symptoms associated with rare clinically significant adverse effects of statins. Symptoms, especially those related to muscles, are the reason for the treatment discontinuation, despite their mild nature and the proven strong benefits of statins in preventing cardiovascular events. Muscle symptoms appear in 5–20% of patients treated with statins according to clinical trial data and usually affect the proximal muscles of the limbs and back, are symmetrical, and may have various other symptoms (pain, cramps, stiffness, weakness). Characteristically, symptoms appear after starting a statin and disappear after stopping its use. Rhabdomyolysis is a rare, serious complication (1–3/100,000 patients/year) characterized by a combination of pain and high levels of CK exceeding 10 times the upper limit of normal. A complication of rhabdomyolysis may be acute kidney injury. Notably, myoglobinuria is currently not a necessary condition for the diagnosis of rhabdomyolysis [46–48].

Muscle-related statin intolerance is defined as an intolerance to at least three different statins, also statins at reduced doses. One of the most important risk factors for muscle symptoms after statins are interactions with commonly used drugs, i.e., fibrates (gemfibrozil), macrolide antibiotics (erythromycin, clarithromycin), antifungal drugs (fluconazole, itraconazole), as well as cyclosporine, amiodarone, verapamil, diltiazapem, amlodipine, nefazodone, danazol, ranolazine, selected protease inhibitors in the treatment of HIV infection. Other factors, such as older age > 75 years, female sex, low body mass index, impaired kidney and liver function, history of muscle ailments, diabetes, HIV infection, type and dose of statin, hypothyroidism, acute infection, low vitamin D3 levels also contribute to the symptoms after statins. The CK determination should be included in the algorithm for the management of muscle symptoms after statins. In the case of 10 fold increase in values above the upper limit, regardless of muscle ailments, the statin should be discontinued and renal function, as well as CK, monitored every 2 weeks until normalization. Subsequently, it is advised to re-include the statin.

In the case of muscle symptoms and elevation of CK 4 to 10 times above the norm, statin withdrawal should be considered until symptoms resolve and CK normalization. After CK normalization, a different statin can be included at a lower dose. If symptoms recur and treatment goals are not achieved, it should be considered to add ezetimibe to a statin followed by a PCSK9 inhibitor. These drugs can also be used as monotherapy [49]. If CK remains elevated, the diagnosis of myopathy and further neurological, endocrine, and rheumatological diagnosis should be considered.

However, in the case of persistent muscle ailments and CK values below 4 times the upper limit, a temporary withdrawal of the statin for a period of 6 weeks may be considered. Subsequently, after the symptoms have resolved, the same or a different statin, at a lower dose, may be used. As an alternative, a regimen of atorvastatin or rosuvastatin at lower doses of 5–10 mg/day, with a frequency of 1–3 times per week, should be considered [4].

The determination of vitamin D3 concentration and compensation for its deficiency, as well as supplementation with coenzyme Q10, may be considered. It should always be determined whether the increase in CK has not occurred after physical activity.

With this approach, more than 90% of people are able to tolerate statins. Therefore, it seems that true statin intolerance affects only a few percent of patients [27]. Particularly, in the case of muscle symptoms after statins, the nocebo effect also plays a dominant role, thus establishing a causal relationship has to be criticized.

Another adverse effect of statins is a mild increase in ALT, which affects 0.5–2% of patients, most often after high-dose potent statins. A clinically significant increase in ALT activity 3 times above the norm requires a temporary withdrawal of the statin until ALT normalizes. However, statin hepatotoxicity has not been proven to be significant, and progression to hepatic failure is extremely rare.

In monitoring patients on high-intensity statin therapy or with insulin resistance, metabolic syndrome, obesity, are contraindicated to forget about periodic glycemic or HbA1c monitoring.

In the case of adverse effects after statins, it is particularly important to educate patients and underline the undeniable benefits of using them and the low risk of direct life-threatening symptoms [4].

9. Non-statin treatment options of dyslipidemia: PCSK9 inhibitors, ezetimibe, fenofibrate, icosapent, inclisiran, and lipoprotein apheresis are an important part of the treatment. Notably, although statin treatment is very effective, it does not always allow achieving the goal lipid levels when administered as monotherapy, even using the most potent statins. When attempting to reach the target LDL-C level, an

alternative approach to increasing the dose and choosing the most potent statin is to add a selective cholesterol absorption inhibitor, ezetimibe, to statin. Following oral administration, ezetimibe binds to the intestinal brush border and selectively inhibits intestinal absorption of cholesterol and plant sterols, which results in reduced cholesterol transport to the liver. In patients with hypercholesterolemia, ezetimibe significantly reduces TC, LDL-C, apoB, and triglyceride levels, and increases HDL-C level. The IMPROVE-IT study showed that the combination of ezetimibe with even one of the oldest statins, simvastatin, led to a much higher number of patients achieving the target LDL-C level, and resulted in a lower high-sensitivity C-reactive protein level compared to patients who received statin monotherapy [50]. In addition, these additional benefits of reduced inflammation translated to better outcomes in patients receiving a combination treatment, with a lower risk of major cardiovascular events and mortality. According to the current European guidelines, ezetimibe is also recommended as an alternative drug in patients intolerant to statins and in patients who do not reach target LDL-C levels despite statin treatment.

Another treatment approach that clearly deserves increasing attention is the use of PCSK9 inhibitors. Their target protein, PCSK9, is involved in the metabolism of LDL receptors (LDLR). An increased PCSK9 level/function reduces LDLR expression by promoting lysosomal catabolism and increases plasma LDL-C level. Available PCSK9 inhibitors, which are monoclonal antibodies against PCSK9, reduce LDL-C level by about 60% regardless of the use of other lipid-lowering therapies [51]. Recent trials with PCSK9 inhibitors showed that very low LDL-C levels achieved with the use of these drugs are associated with a reduced cardiovascular event rate and a reduction of atherosclerotic lesions (plaque volume) in coronary arteries [52–54]. Candidates for this treatment are patients at a very high total cardiovascular risk, subjects with HeFH (and also some subjects with homozygous FH) receiving maximum tolerated doses of first and second-line drugs and/or treated with apheresis, and those intolerant to statins, in whom LDL-C levels are persistently high. Nevertheless, despite the proven effectiveness of PCSK9 inhibitors, wider use of this modern therapy is hampered by economic barriers and lack of reimbursement except for two drug programs — their range has recently been significantly expanded, which gives hope that Polish patients, similarly to patients in other European countries, will have access to this modern therapy.

A very promising therapeutic option for patients with primary hypercholesterolemia and mixed dyslipidemia is inclisiran registered in December 2020 in Europe. This drug belongs to the siRNA group and inhibits the synthesis of the PCSK9 protein in the liver. Inclisiran has been shown in ORION clinical trial to reduce LDL-C by approximately 50% with a low percentage of adverse effects, mainly related to injection site reactions (1 per 10 people). It should be underlined that the dosage of the drug is revolutionary in lipid-lowering drugs — it is administered twice a year, which solves the problem of non-compliance — one of the most important issues with statins.

It should be remembered that in patients with atherogenic dyslipidemia, statin monotherapy does not fully protect them from cardiovascular events. In these patients, the optimal therapy, particularly with concomitant diabetes or metabolic syndrome, is a combination of a statin and fenofibrate which helps achieve the secondary treatment goal of non-HDL-C level normalization [55]. The recently published results of the ACCORDION study suggest a possible effect of fenofibrate added to a statin on the reduction of long-term total mortality in diabetics [56].

If isolated severe hypertriglyceridemia is present, treatment is started with fibrate monotherapy, which is also a prevention of acute pancreatitis.

For patients with triglyceride levels of 135–499 mg/dL in the high and very high-risk categories, the use of omega-3 unsaturated fatty acids (eicosapentaenoic acid ethyl ester 2 × 2 g/d) in combination with statins should be considered. These drugs can lower triglyceride levels by as much as 30–45%.

As revealed in the REDUCE-IT study, icosapent (eicosapentaenoic acid ethyl ester, unavailable in Poland) used in a dose of 2 g twice a day in combination with a statin significantly reduced the risk of cardiovascular events and lowered triglyceride level by 18%. These data cannot be extrapolated to other doses and other omega-3 preparations, in general not showing an effect on clinical adverse events. Therapy with omega-3 acids is safe, and the adverse effects comprise mainly gastrointestinal disorders [4].

The last form of treatment that should be mentioned here is lipoprotein apheresis. Lipoprotein apheresis is a very effective procedure for extracorporeal purification of the blood or plasma from LDL, very-low-density-lipoprotein and Lp(a)

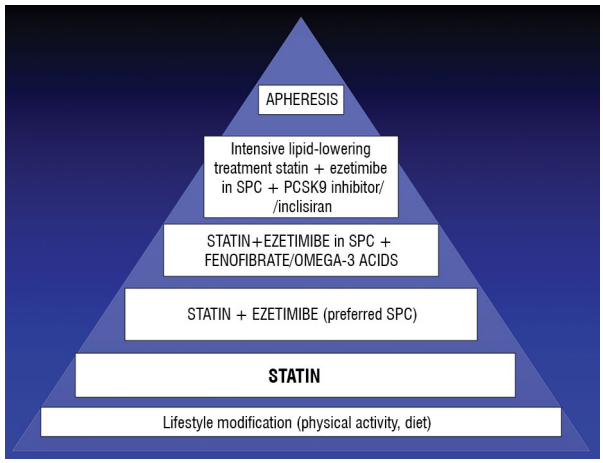

Figure 4. Pyramid of lipid-lowering pharmacotherapy; PCSK9 — proprotein convertase subtilisin/kexin type 9; SPC — single-pill combinations.

particles, but it must be systematically repeated every 1–2 weeks. About 60–80% of LDL-C and Lp(a) can be removed at one time. Lipoprotein apheresis should be considered in patients who, despite the maximum dose of hypolipidemic drugs and diet, still have LDL-C levels above the recommended target. However, it is currently a therapy dedicated rather to patients with a high concentration of Lp(a) > 100 mg/dL and with ASCVD.

In conclusion, the basis for lipid profile modification and treatment interventions in dyslipidemia is graphically summarized on a lipid-lowering therapy pyramid (Fig. 4). Physical activity and lifestyle modification, and subsequently — statin treatment, statin treatment in combination with another lipid-lowering drug (ezetimibe/fenofibrate/ /omega-3 acids) and eventually supplementing the pharmacotherapy with another modern lipid-lowering drug (PCSK9 inhibitors/inklisiran) are the standard of patient care. PCSK9 inhibitors, alirocumab, and evolocumab have already been introduced into routine treatment in drug programs in two indications: certain clinical diagnosis of FH and after myocardial infarction (detailed criteria are described in point 10 of the Declaration).

10. With advances in medicine and drug therapy, it is possible to achieve a significant improvement of the effectiveness of dyslipidemia treatment in Poland. Nonetheless, as mentioned in the introduction, therapeutic goals of dyslipidemia treatment continue to be achieved at an unsatisfactory rate, only slightly above 10%, also among high-risk patients. It is thus particularly important to identify the reasons for this poor dyslipidemia control in our country. The most common errors of statin therapy include therapeutic nihilism, statin doses that are too low, statins that are too weak, and treatment discontinuation in case of muscle symptoms occurrence after statins [57]. Although lipid-lowering treatment should mostly be continued indefinitely in patients with established cardiovascular disease, in many of them the statin dose is reduced (usually after a follow-up testing shows that the target LDL-C level has been achieved) or the drug is discontinued.

Recently, with advances in drug therapy, new therapeutic options have become available which may potentially improve patient compliance and at least partially reduce difficulties with achieving target lipid levels. Most notably, these include intermediate statin doses (rosuvastatin 15 and 30 mg) which allow fine tuning of the intensity of the lipid-lowering effect and determining the optimal dose for a given patient and single-pill combinations (SPC). The latter in particular has been a major breakthrough on the pharma market. Currently, the following SPC containing two lipid-lowering drugs in one tablet are available in Poland:

— atorvastatin and ezetimibe;
— rosuvastatin and ezetimibe.

Particularly important is the appearance on the market of SPC rosuvastatin and ezetimibe, which contains the highest permitted doses of these drugs (SPC R/E 40/10).

According to a new statement of the European Atherosclerosis Society (EAS) working group, in the group of patients who suffered from ASCVD with LDL-C concentration ≥ 100 mg/dL, who have not previously received lipid-lowering therapy (including statins in monotherapy), combination therapy with a high-intensive statin with ezetimibe is recommended as first-line therapy (Fig. 5) [58]. However, the priority of achieving the maximum tolerated dose of statins should be remembered.

In addition, it should be noted that since 2019, a treatment program of FH with PCSK9 inhibitors has been implemented in Poland. These drugs are fully reimbursed if specific criteria are met. Two preparations of PCSK9 inhibitors are available in Poland: alirocumab and evolocumab. These drugs constitute the third line of hypercholesterolemia treatment and the status after myocardial infarction when the current treatment with a statin (first-line drug) and ezetimibe (second-line drug added to a statin) does not achieve the treatment goal recommended by the physician.

Inclusion criteria in the FH drug treatment program (all criteria must be met):

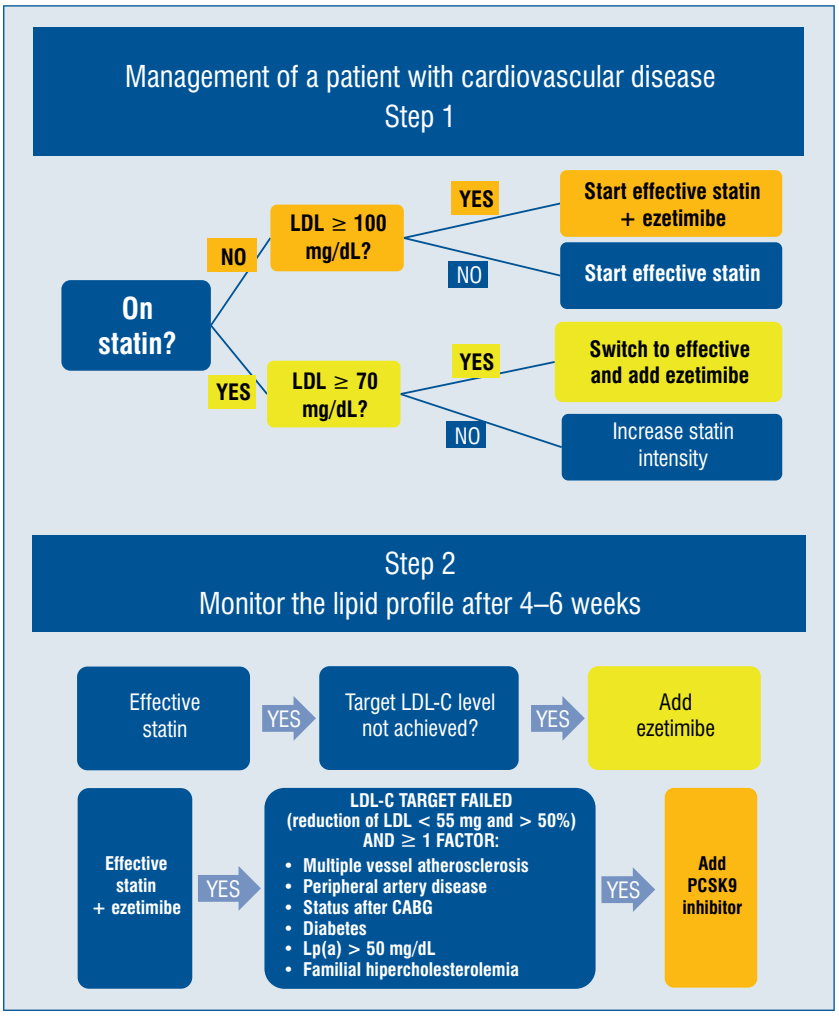

Figure 5. A new dyslipidemia treatment algorithm proposed by the European Atherosclerosis Society (EAS) 2021 (adapted from: [58], modified); LDL — low density lipoprotein; LDL-C — low density lipoprotein cholesterol; CABG — coronary artery bypass grafting; Lp(a) — lipoprotein (a); PCSK9 — proprotein convertase subtilisin/kexin type 9.

1) age ≥ 18 years;
2) certain diagnosis of HeFH, i.e. > 8 points in the DLCN scale;
3) meeting the eligibility criteria for LDL apheresis treatment, and for patients already treated, meeting these criteria at initiation of LDL apheresis treatment;
4) eligibility criteria for LDL apheresis: LDL-C > 100 mg/dL (2.5 mmol/L) despite diet and:
   a) intensive statin therapy at maximum doses, i.e. atorvastatin 80 mg or rosuvastatin 40 mg, followed by atorvastatin 40–80 mg or rosuvastatin 20–40 mg in combination with ezetimibe 10 mg; used for a total of 3 months, including combination therapy for a minimum of 1 month

   or

   b) intensive statin therapy at maximum tolerated doses, followed by combination therapy with ezetimibe 10 mg, for a total of 3 months, including combination therapy for a minimum of 1 month.

In addition, in recent months, the program has been extended to include patients with a very high risk of cardiovascular diseases. Criteria for inclusion in the drug program of patients with very high cardiovascular risk (all of the following must be met):

1) age ≥ 18 years;
2) LDL-C > 100 mg/dL (2.5 mmol/L) despite diet and intensive treatment with statins at the maximum tolerated doses, followed by statins at the maximum tolerated doses in combination with ezetimibe. A total treatment period

of at least 3 months is required, including at least 1 month of combination therapy (statin at maximum tolerated doses + ezetimibe). For patients with suspected statin-related rhabdomyolysis, the treatment period is determined by the treating physician in accordance with the guidelines of the European Society of Cardiology (ESC)/EAS;

3) a history of invasively diagnosed myocardial infarction, which occurred up to 12 months before enrollment in the drug program, and
   a) with an additional history of myocardial infarction and multivessel coronary artery disease, defined as ≥ 50% stenosis in ≥ 2 vessels
   or
   b) with atherosclerotic disease of non-coronary arteries, understood as:
      - peripheral artery disease, i.e.:
        — intermittent claudication with ankle-brachial index < 0.85,
        or
        — previous revascularization of peripheral arteries,
        or
        — limb amputation due to atherosclerotic disease;
        or
      - cerebral artery disease, i.e.:
        — previous ischemic stroke,
        or
        — transient ischaemic attack.

Patients who are currently treated with evolocumab or alirocumab and who were eligible for the drug program at the time of initiation of the treatment with evolocumab or alirocumab and who did not meet the criteria described in section 3 may also be qualified for the drug program to ensure treatment continuation.

11. Lipid-lowering treatment is significant in the COVID-19 pandemic era. Ever since the outbreak of the pandemic, it was underlining that chronic treatment of dyslipidemia should be continued in every subject infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, the pandemic resulted in a confirmed deterioration in the control of cardiovascular risk factors, an increase in therapeutic inertia, and the ignoring of the necessary control of effects and the need for treatment escalation. There were studies suggesting that the additional immunomodulatory and anti-inflammatory properties of statins may aid in the treatment of COVID-19. However, such data have not yet been verified in controlled, prospective clinical trials. Retrospective studies show the benefits of statins in COVID-19 patients, which could be based on their:

- anti-inflammatory effect (reducing the concentrations of interleukin [IL] 6, IL-8, affecting the activation of T lymphocytes);
- anticoagulant effect (increase in nitric oxide excretion, improvement in endothelial function, effect on platelet aggregation, decrease in the production of type 1 plasminogen activator inhibitor);
- potential effect of reducing SARS-CoV-2 virus entry (several contradictory theories related to modifying the composition of cell membranes);
- potential effect on angiotensin converting enzyme 2 (ACE2) expression;
- other mechanisms, e.g. the described inhibitory effect of statins on Mpro — the main protease of SARS-CoV-2 virus (it is not known whether the levels of statins present in the body have this effect).

Limited access to a physician should force appropriate modifications to the present treatment algorithms so that a patient with dyslipidemia, in the COVID-19 era, receives effective treatment as soon as possible, which could be continued in the teleconsultation system. Therefore, it seems rational to shorten the procedure algorithms as much as possible, even when it is not officially recommended by the scientific society. It seems that effective treatment should be given as soon as possible, especially in groups of high, very high, and extremely high cardiovascular risk patients. Thus, an approach may be considered in which, for example, an injection to lower LDL-C (PCSK9 inhibitors) should be administered with a statin on the first day of treatment, upon admission. Such administration of evolocumab (the best tested PCSK9 inhibitors in acute myocardial infarction) ensures that normolipemia (correct, target LDL-C is achieved already during hospitalization instead of many weeks after leaving the hospital. Likewise, a patient with high cardiovascular risk and a high baseline LDL-C level should, in principle, receive the statin and ezetimibe combination straight away, rather than waiting several weeks for the effectiveness of the statin to be determined. This reasoning is presented in the three models below, which are a specific interpretation of the current treatment guidelines in Europe.

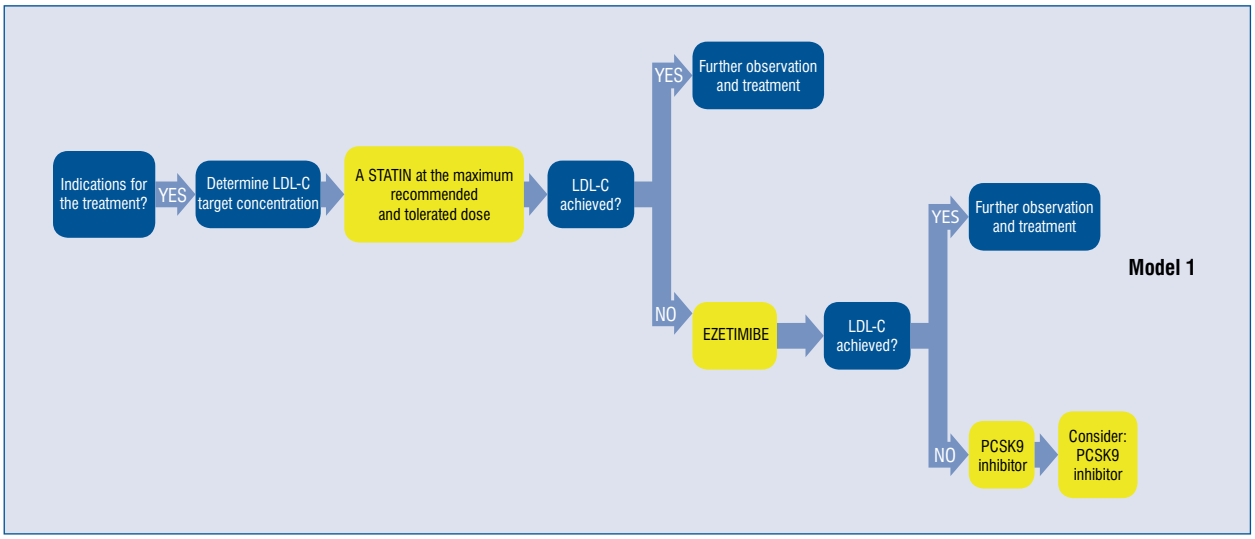

Figure 6. The first model — a three-stage algorithm for the treatment of hypercholesterolemia, promoted and in force for cardiologists from 2019 in Europe; mandatory model in 2020, developed by European Society of Cardiology (ESC) (adapted from: [4], modified); LDL-C — low density lipoprotein cholesterol; PCSK9 — proprotein convertase subtilisin/kexin type 9.

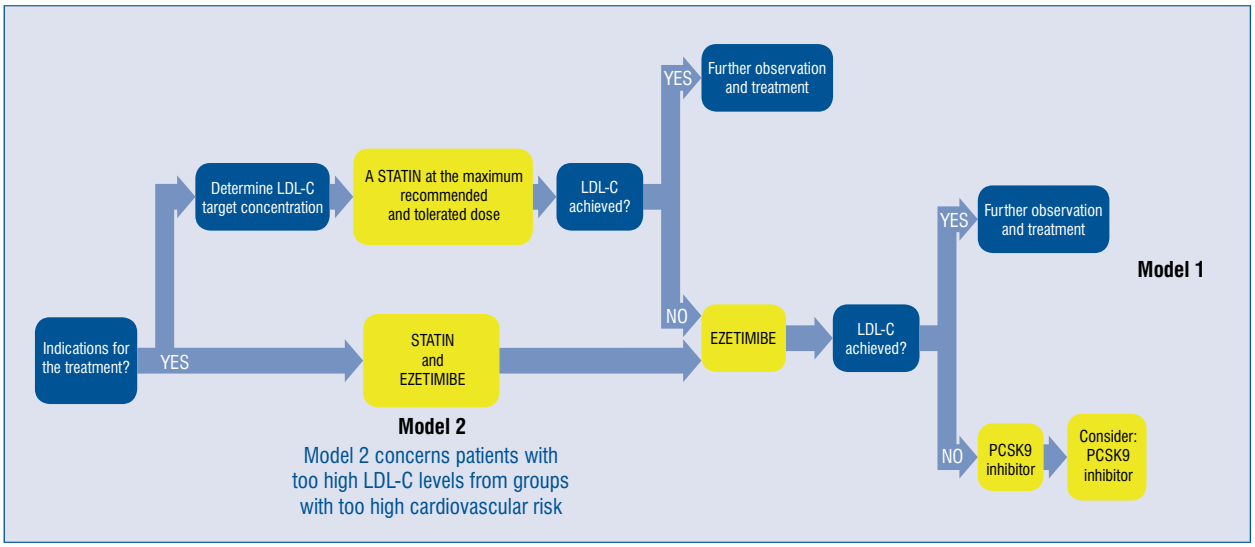

Figure 7. The second model — accelerated algorithm for possible treatment with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor; developed on the basis of the European Society of Cardiology (ESC) model from 2020 (adapted from: [4], modified) by Krzysztof J. Filipiak; LDL-C — low density lipoprotein cholesterol.

The first model (Fig. 6) [4] is based on the current guidelines of the European Society of Cardiology and recommends starting therapy with a statin, adding ezetimibe (a second oral drug with a different mechanism of action) after a few weeks, and in case of treatment failure — the introduction of additional injections of a PCSK9 inhibitors.

In the current situation, in the era of COVID-19, it is not possible, in many cases, to wait a few weeks for achieving the lipid target (problem with contact with the ordering physician or family physician), it is also not worth starting treatment in patients with even the highest dose of a statin when we know that it will not achieve the lipid target anyway. In such cases, it is worth using the second model — accelerate the algorithm — administer a statin with ezetimibe immediately and check in a few weeks whether the addition of a PCSK9 inhibitors is required (Fig. 7).

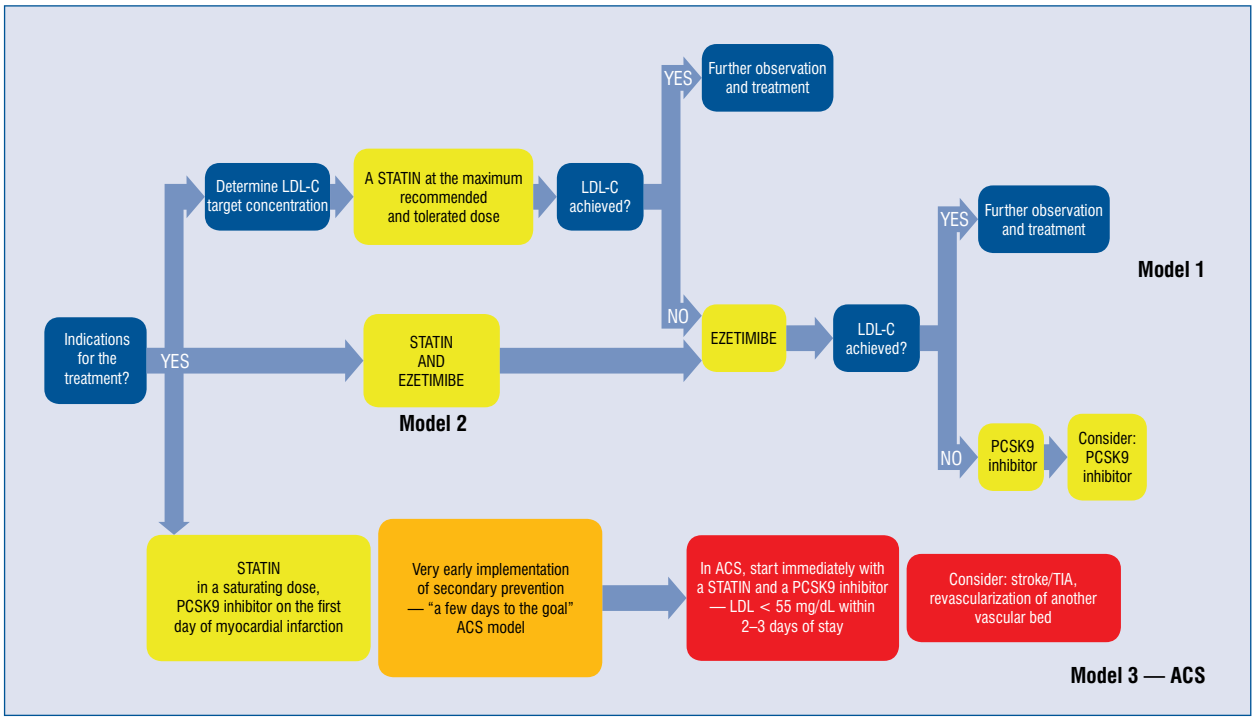

Figure 8. The third model — proposed therapeutic management for patients with acute coronary syndromes (ACS) — early administration of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor simultaneously with a statin; developed on the basis of the European Society of Cardiology (ESC) model from 2020 (adapted from: [4], modified) by Krzysztof J. Filipiak; the model to be considered also in other patients in the future — those with stroke, transient ischemic attack (TIA) of the central nervous system, revascularization of another vascular bed; LDL-C — low density lipoprotein cholesterol.

However, it seems that this is insufficient for the highest-risk patients — such as those with acute myocardial infarction. Based on the EVOPACS and EVACS studies with evolocumab, we can currently postulate that the combined administration of a high dose of a statin and an injection of evolocumab immediately upon admission to the hospital. Some experts see no space for ezetimibe here anymore. The combination of a statin and evolocumab allows the majority of treated patients to achieve optimal LDL-C < 55 mg/dL already during the 3–4-day of hospitalization. It was the basis of the third model we proposed for patients with acute coronary syndromes (Fig. 8).

The proposed, modified management algorithms could facilitate the care of patients with dyslipidemia in the times of COVID-19. Limited contact with a physician is not conducive to optimal care, it hampers the implementation of the drug program with PCSK9 inhibitor dedicated to patients with FH, as well as the new drug program with PCKS9 inhibitor dedicated to patients at high cardiovascular risk, which is to enter into practice in the last months of 2021.

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Cardiac implantable electronic devices procedures and their recipients characteristic during COVID-19 pandemic: 3.8 million population analysis

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Abstract

Background: *Coronavirus disease 2019 (COVID-19) pandemic disorganised healthcare systems and has caused a reduction in the number of hospitalizations and procedures. Cardiac implantable electronic device (CIED) procedure rates and clinical characteristics of their recipients were compared in corresponding weeks of 2019 and 2020 were analyzed.*

Methods: *The database of the National Health Fund (NHF) in Poland was retrospectively analyzed. 3206 patients who underwent CIED implantation in the Silesia — a region in Southern Poland comprising an adult population of 3.8 million between 12th and 31st week of 2020. Patients were classified into groups: the recipient of an implantable cardioverter-defibrillator or cardiac resynchronization therapy group (ICD/CRT) or pacemaker group (PM).*

Results: *During the pandemic a reduction of 39.38% of implantations was observed compared to the same period in 2019 (1210 vs. 1996 patients) and had impacted both groups. Two phases lasting 10 weeks each could be distinguished: total lockdown (maximal reduction) and the recovery phase with growing numbers of procedures. Patient baseline characteristics (sex, age, comorbidities) who were implanted during the COVID-19 pandemic did not differ from the 2019 period. The rate of peri-procedural mortality was also similar.*

Conclusions: *During COVID-19 pandemic period a reduction in CIED implantations of all types was observed. Despite the decreased number of performed CIED implants, no differences in baseline patient characteristics were observed.* (Cardiol J 2022; 29, 1: 27–32)

Key words: COVID-19, cardiac implantable electronic devices, pacemakers, implantable cardioverter-defibrillator, cardiac resynchronization therapy, pandemic

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Introduction

The pandemic caused by severe adult respiratory system coronavirus-2 (SARS-CoV-2 [COVID-19]) forced major changes of healthcare systems worldwide. Numerous elective admissions were revoked or postponed and in-hospital treatment focused mainly on acute cases, substantial resources were used to fight the infection. This issue also concerns the patients planned for cardiac implantable electronic devices (CIED) procedures and may affect a patient's profile. Governmental regulators, insurance companies, as well as national and international professional societies published several rules or recommendations which should be or are advised to be implemented during the pandemic [1, 2]. In Poland the regulator of the National Health Fund (NHF) on March 13th, 2020, as well as the Heart Rhythm Association of Polish Cardiac Society (March 26th, 2020) strongly advised performing only urgent procedures: implantation of a pacemaker (PM) due to the second- or third-degree atrioventricular block, placement of implantable cardioverter-defibrillator (ICD) in the secondary prevention of sudden cardiac death, exchange of pacing systems and ICDs due to battery depletion or damage to the leads, removal of pacing/defibrillation systems because of infections and ablations of incessant and resistant to other forms of treatment life-threatening supraventricular arrhythmias as well as dangerous recurrent chronic ventricular arrhythmias [2]. In parallel, low symptomatic patients even classified in the abovementioned categories were afraid to be hospitalized even in a non-COVID-19 hospital so they will to postpone the procedure.

The aim of the analysis was to evaluate the changes in implantation rates and clinical characteristics of CIED candidates before and during the COVID-19 pandemic.

Methods

A retrospective analysis with the use of an NHF database, the only public insurance company in Poland, was performed. Data were collected from the Silesian Cardiovascular Database (SILCARD), which contains records from 310 hospitals located in Silesia, a large, urbanized region in Southern Poland populated with 3.8 million adults (a total of 4.5 million — 11.8% of Poland's population). The SILCARD database is obtained from the NHF and contains raw, anonymized data: the principal diagnosis with up to three comorbidities, type of implanted CIED, administrative and epidemiological pieces of information. Silesia contains a well-developed hospital network, with two tertiary cardiology teaching hospitals and 22 implantation laboratories (Fig. 1). General information on SILCARD was previously reported [3]. In short, the SILCARD database enrolled all consecutive Silesian adult patients hospitalized in cardiology and cardiac surgery units for cardiovascular disease (CVD). Patients living outside of Silesia and patients younger than 18 years at the time of admission were excluded. The hospitals are reporting a principal diagnosis with up to three comorbidities as defined by the 10th revision of the International Classification of Disease (ICD-10) classification for every hospitalization and medical procedure codes (ICD-9). CVD was defined as any "I" code according to the ICD-10. For implantation identification, code Z45.0 was used in parallel with procedure code for the first implantation of the appropriate device. All vulnerable data were anonymized. The local Ethics Committee approved the use of the SILCARD registry. Based on the information received from the NHF, data from pre-specified periods were analyzed. The three periods were defined as the following: pre-pandemic (2nd – 11th week), lockdown (12th – 21st week), stepdown (22nd – 31st). The ICD-10 codes have been reported to the NHF since the beginning of the registry's existence to current hospitalizations. Because of the type of investigation, consent from patients was waived.

Patient analysis

De-novo, device implantations of PM, ICD and cardiac resynchronization therapy (CRT) devices were analyzed, but the urgency of the procedure (urgent or elective) was not differentiated. Generator replacements were excluded from the analysis, because these patients were classified as urgent cases and the regulator did not recommend postponing procedures. Patients who received devices were classified into two groups according to the device type: ICD/CRT or PM.

Time analysis

Firstly, a direct comparison of pandemic phase from 12th to 31st week of 2020 was compared with the same phase in 2019. Secondly, after examining weekly trends, the pandemic phase was broken into two: complete lockdown (weeks 12th – 21st) and step-down, recovery phase (weeks 22nd – 31st) and compared them not only to corresponding weeks in 2019 but also to same length in the pre-pandemic phase (2nd – 11th week of 2020).

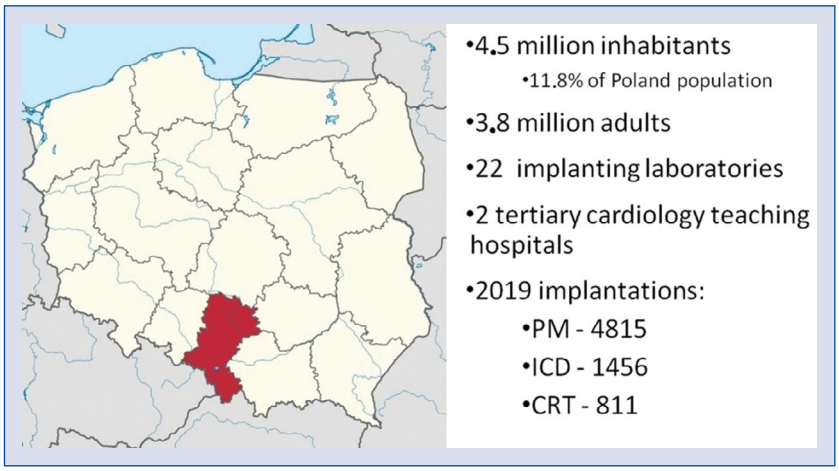

Figure 1. Silesia voivodeship population and 2019 implantations. CRT — cardiac resynchronization therapy; ICD — implantable cardioverter-defibrillator; PM — pacemaker.

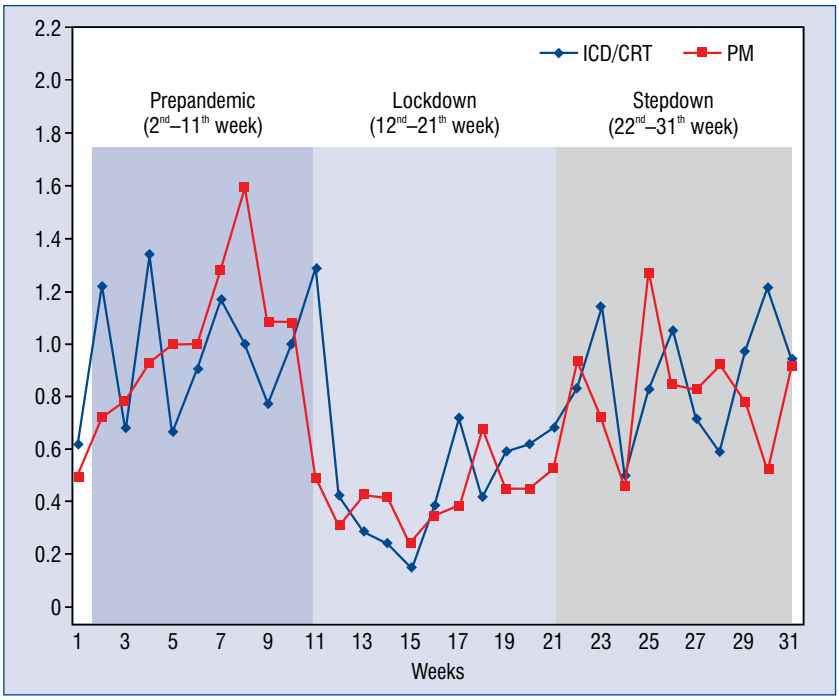

Figure 2. Implantation rate of implantable cardioverter-defibrillator/cardiac resynchronization therapy (ICD/CRT) and pacemaker (PM) as a ratio of 2020/2019 numbers for consecutive weeks 1 to 31.

Statistical analysis

Continuous variables are presented as the median with interquartile range due to non-normal distribution. Categorical variables were expressed as frequencies and percentages. Statistical analysis was performed with the χ^2 test or U Mann-Whitney test as appropriate. A two-sided p-value < 0.05 was considered significant. The SAS software, version 9.4 (SAS Institute Inc., Gary, NC) was used for all calculations.

Results

Overall, data from patients who underwent CIED implantation from the 12th to 31st week were analyzed. The number of implantation procedures during the COVID-19 period decreased by 39.38% compared to the same period in 2019 (1210 vs. 1996 patients). The reduction concerned both types of devices: ICD/CRT group: decrease of 35.81% (423 vs. 659); PM group: decrease of 41.14% (787 vs. 1337) (Fig. 2).

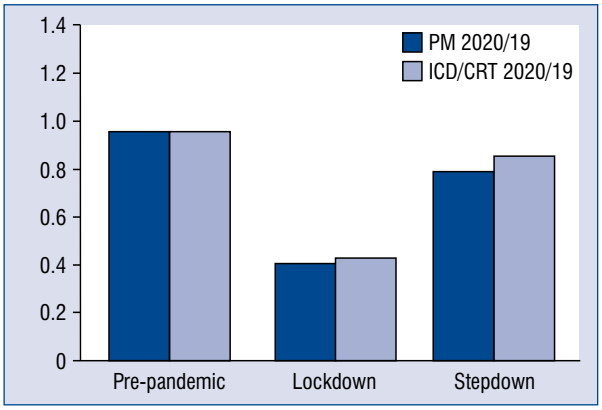

Figure 3. Comparison of implantation rates of pacemaker (PM) and implantable cardioverter-defibrillator/cardiac resynchronization therapy (ICD/CRT) as a ratio of 2020 and 2019 numbers for the three 10-week periods: pre-pandemic (2nd–11th week), lockdown (12th–21st week) and stepdown (22nd–31st).

After the end of the first wave of the pandemic (complete lockdown) since June 2020, the number of implantations gradually increased, and almost reached pre-pandemic levels. The most noteworthy drop was between 12th to 21st week of 2020: all patients — a decrease of 54.74% (506 vs. 1118); ICD/CRT group — a decrease of 53.95% (163 vs. 354); in PM group — a decrease of 55.1% (343 vs. 764). Pre-pandemic data of 2020 (2nd to 11th week) corresponded with 2019 numbers (ICD/CRT 347 vs. 364, PM 688 vs. 719). The data from the final 10-week period — partial recovery (22nd to 31st week) showed a higher number of implantations: greater in ICD/CRT (286 vs. 334), also important, but was less pronounced in PM group (495 vs. 626) (Fig. 3).

The clinical characteristics of the CIED recipients from 2019 and 2020 were similar in both groups (Tables 1, 2). No significant differences were found in age, sex, symptoms, heart disease and comorbidities. Moreover, the in-hospital mortality related to implantation procedures was also similar.

Discussion

In Poland a national lockdown was implemented on March, 14th, 2020. Worldwide, the COVID-19 pandemic decreased the number of elective and urgent cardiac procedures. The decline was expressed especially in the first weeks after the lockdown was introduced. In Italy, in the Veneto region, a significant decrease in the number of urgent PM implantations was observed during the 6 weeks after the COVID-19 outbreak [4]. In Peru, in the national reference hospital, the largest in the country, a reduction in the de-novo PM implant was 73% (95% confidence interval [CI] 33–113; $p < 0.001$), observed during the COVID-19 pandemic [5]. Marini et al. [6] showed that the clinical characteristics of urgent CIED recipients remained the same despite the COVID pandemic. Results of present analysis are in line with these

Table 1. Clinical characteristics of implantable cardioverter-defibrillator/cardiac resynchronization therapy recipients in the compared periods of 2019 and 2020.

	Year		P
	2019	2020	
Number of patients	659	432	
Age, median (Q1, Q3)	68.9 (62; 75)	68.2 (61; 74)	0.425*
Male gender	521 (79.1%)	336 (79.4%)	0.939
Hypertension	401 (60.8%)	260 (61.5%)	0.848
Diabetes	175 (26.6%)	115 (27.2%)	0.833
Previous PCI	359 (54.5%)	219 (51.8%)	0.417
Previous CABG	74 (11.2%)	65 (15.4%)	0.051
Previous MI	269 (40.8%)	173 (40.9%)	1.000
Chronic kidney disease	49 (7.4%)	21 (4.9%)	0.128
History of AF	208 (31.6%)	143 (33.8%)	0.464
Peri-procedural mortality	2	1	0.838

*U Mann-Whitney test, the remaining χ^2 test; AF — atrial fibrillation or flutter; CABG — coronary artery bypass grafting; MI — myocardial infarction; PCI — percutaneous coronary intervention

Table 2. Clinical characteristics of pacemaker recipients in compared periods of 2019 and 2020.

	Year		P
	2019	2020	
Number of patients	1337	787	
Age, median (Q1, Q3)	77.2 (70; 83)	77.8 (71; 83)	0.209*
Male gender	653 (48.8%)	381 (48.4%)	0.584
Hypertension	709 (53.0%)	433 (55.0%)	0.392
Diabetes	262 (19.6%)	147 (18.7%)	0.649
Previous PCI	244 (18.2%)	149 (18.9%)	0.729
Previous CABG	75 (5.6%)	35 (4.4%)	0.266
Previous MI	160 (12.0%)	101 (12.8%)	0.584
Chronic kidney disease	74 (5.5%)	42 (5.3%)	0.921
History of AF	387 (28.9%)	228 (29.0%)	1.000
Peri-procedural mortality	5 (0.4%)	9 (1.1%)	0.034
Yates corr. 0.066			

*U Mann-Whitney test, the remaining χ^2 test; AF — atrial fibrillation or flutter; CABG — coronary artery bypass grafting; MI — myocardial infarction; PCI — percutaneous coronary intervention

observations. There are several explanations for the decrease in the number of CIED implantations. First, the fear of getting the COVID-19 infection unmotivated those looking for medical attention even for severe symptoms. The fear also leads to postponing previously planned procedures in low symptomatic cases. This fear has been reported in a study of psychological responses to emerging outbreaks of infectious diseases [7] and reduced admissions for acute coronary syndromes and reduction in primary percutaneous coronary interventions [8]. The German Helios network study revealed a deficit of hospitalizations due to several categories of CVD during the pandemic [9].

Another reason could be transitory impeded access to medical healthcare. It is not only about hospital emergency departments, where the most symptomatic patients come. The system may have missed asymptomatic or mildly symptomatic patients who had limited access to outpatient clinics and professional societies published several documents on how to deal with different categories of patients during the pandemic, advising to postpone elective cases [1, 2]. The Italian Society of Arrhythmias and Cardiac Pacing survey revealed a significant reduction of procedures including not only urgent PMs but also of ICD implantations for primary, as well as secondary prevention in a majority of hospitals [10].

It is worth emphasizing that in the present analyses the total number of implanted generators, not only urgent cases were examined. In the first weeks after the national lockdown was introduced, the decline of implantations was very visible. Probably, during this period, only urgent, life-saving procedures were performed. In the following weeks, when both patients and medical healthcare got used to pandemic conditions (e.g., nosocomial procedures for testing, isolation and disinfection), progressive recuperation was observed, and elective implantations have been reintroduced. Interestingly, it seems that ICD/CRT implants number grew faster than PM. Finally, the in-hospital mortality related to implantations procedures was comparable. At the level of statistical significance, the peri-procedural death was higher during pacemaker implantations during the COVID-19 period. It is conceivable that higher mortality resulted from more severe baseline condition of patients who delayed admission to hospital and possible COVID-19 co infection.

Limitations of the study

Lack of differentiation between types of hospital. Types of procedure and peri-procedural complications may vary between COVID-19 and non-COVID-19 hospitals as well as between tertiary teaching hospitals vs. implantation laboratories.

Cardiac implantable electronic device replacement procedures were excluded from the analysis.

Lack of differentiation between urgent and elective procedures.

Data about procedures performed in COVID-19 patients are not available.

Conclusions

During the COVID-19 pandemic period a reduction in CIED implantation of all types was observed. Despite the decreased number of performed CIED implants, no differences in baseline patient characteristics were observed.

Conflict of interest: None declared

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Outcomes and mortality associated with atrial arrhythmias among patients hospitalized with COVID-19: A systematic review and meta-analysis

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Abstract

Background: *Atrial fibrillation (AF) is the most common cardiac arrhythmia in the adult population. Herein, is a systematic review with meta-analysis to determine the impact of AF/atrial flutter (AFL) on mortality, as well as individual complications in patients hospitalized with the coronavirus disease 2019 (COVID-19).*

Methods: *A systematic search of the SCOPUS, Medline, Web of Science, CINAHL and Cochrane databases was performed. The a priori primary outcome of interest was in-hospital mortality. A random-effects model was used to pool study results.*

Results: *Nineteen studies which included 33,296 patients were involved in this meta-analysis. In-hospital mortality for AF/AFL vs. no-AF/AFL groups varied and amounted to 32.8% vs. 14.2%, respectively (risk ratio [RR]: 2.18; 95% confidence interval [CI]: 1.79–2.65; $p < 0.001$). In-hospital mortality in new onset AF/AFL compared to no-AFAFL was 22.0% vs. 18.8% (RR: 1.86; 95% CI: 1.54–2.24; $p < 0.001$). Intensive care unit (ICU) admission was required for 17.7% of patients with AF/AFL compared to 10.8% for patients without AF/AFL (RR: 1.94; 95% CI: 1.04–3.62; $p = 0.04$).*

Conclusions: *The present study reveals that AF/AFL is associated with increased in-hospital mortality and worse outcomes in patients with COVID-19 and may be used as a negative prognostic factor in these patients. Patients with AF/AFL are at higher risk of hospitalization in ICU. The presence of AF/AFL in individuals with COVID-19 is associated with higher risk of complications, such as bleeding, acute kidney injury and heart failure. AF/AFL may be associated with unfavorable outcomes due to the hemodynamic compromise of cardiac function itself or hyperinflammatory state typical of these conditions.* (Cardiol J 2022; 29, 1: 33–43)

Key words: atrial fibrillation, atrial flutter, new onset atrial fibrillation, COVID-19, outcome, systematic review, meta-analysis

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Introduction

Cardiovascular diseases (CVD) are known to affect the prognosis of patients hospitalized with coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) [1, 2]. It has been demonstrated that patients with pre-existing comorbidities, e.g., hypertension, coronary artery disease (CAD) or congestive heart failure are more likely to suffer from the severe course of COVID-19 [3, 4], more often require admission to the intensive care unit (ICU) [4–6], use mechanical ventilation [3, 7] and have higher mortality [3, 7, 8], compared to patients without CVD. This is a sign of increased vulnerability towards the virus and subsequent disease.

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the adult population. According to European Society of Cardiology, global prevalence of AF oscillates between 2% and 4% and is expected to further increase due to longevity, including an expanding group of people with long-lasting underlying CVD [9]. The incidence of atrial flutter (AFL) in individuals without recent predisposing events and preexisting comorbidities is estimated to reach 1.7% [10]. Pathophysiological mechanisms responsible for those arrhythmias include i.e.: structural and electrical atrial remodeling through fibrosis, hypertrophy, inflammation or oxidative stress [9, 11, 12]. Acute inflammation in the course of COVID-19 may alter atrial electrophysiology and structural substrates, therefore playing a major role in the development of these conditions in patients with COVID-19 [13]. Due to the well-established links between inflammation and AF, the association between COVID-19 and AF constitutes an interesting and thus far, unexplored subject.

Outcome analysis of patients hospitalized with COVID-19 provides valuable data that can generate new hypotheses regarding the pathophysiology of AF and AFL, help to identify patients at a higher risk for adverse outcomes and improve patient management within hospital wards. Previously published literature on the outcomes of COVID-19 patients with AF/AFL consists mainly of retrospective studies, rarely single-center prospective ones and very often provides conflicting results. This problem has previously been addressed in the "discussion forum" section of European Heart Journal [14, 15] or in review articles [16].

However, to reach solid conclusions regarding the association between AF/AFL and outcomes of patients with COVID-19, a systematic analysis of available data is indispensable. The available research is insufficient, with one meta-analysis published in January 2021, providing data about the influence of AF on outcomes of patients with COVID-19 [17]. However, it only evaluated the mortality outcomes, without considering other complications, and it has been limited to the European and United States populations. Furthermore, due to the constant changes in our understanding of COVID-19, development of new treatment protocols and pandemic dynamics itself, it is essential to provide updated, high-quality data regarding the association between COVID-19 and CVD. A systematic review with meta-analysis was performed herein, to determine the impact of AF/AFL on mortality, as well as individual complications in patients hospitalized with COVID-19.

Methods

The current systematic review and meta-analysis was complied with the widely recognized Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (**Suppl. Table S2**) [18]. Due to the study design, neither an institutional review board approval nor patient informed consent were required.

Search strategy

An extensive search was conducted of the relevant data using the SCOPUS, Medline, Web of Science, CINAHL and the Cochrane Central Register for Controlled Trials from these databases inception through to October 10th, 2021. The search was performed using the following terms: "atrial fibrillation" OR "AF" OR "atrial flutter" OR "AFL" AND "COVID-19" OR "coronavirus disease 2019" OR "SARS-CoV-2". Two of the reviewers (M.P. and A.G.) independently selected candidates for the study, and conflicts were resolved through discussion with a third reviewer (L.S.).

Studies comparing adult COVID-19 patients more than 18 years old with and without AF/AFL were systematically searched as noted. All randomized controlled trials (RCTs) and observational studies were included in this review. Case reports, case series, and conference abstracts were excluded.

Data extraction

Two reviewers (L.S. and M.P.) independently assessed each article to determine whether they met the inclusion criteria. In cases of suspected

data discrepancies, the relevant author was contacted directly, moreover, care was taken to avoid including data from duplicate publications.

Primary and secondary outcomes

The a priori primary outcome of interest was in-hospital mortality. Secondary outcomes were: occurrence of adverse events, in-hospital cardiovascular death or hospital- or ICU-length of stay.

Risk of bias assessment

Risk Of Bias In Non-randomized Studies was used — the Interventions (ROBINS-I) tool was utilized to assess the quality of the studies' design and extent of potential bias [19]. The ROBINS-I tool examines five bias domains: (1) bias due to confounding; (2) bias due to selection of participants; (3) bias in classification of interventions; (4) bias due to deviations from intended interventions; (5) bias due to missing data; (6) bias in measurement of outcomes; (7) bias in selection of the reported result. The overall ROBINS-I judgment at domain and study level was attributed according to the criteria specified in the ROBVIS tool [20].

Statistical analysis

The Cochrane Statistical Package Review Manager ver. 5.4 (Cochrane Collaboration, London, United Kingdom) was used for data synthesis and analysis. For dichotomous data, odds ratios (ORs) or risk ratios (RRs) as the effect measure were used with 95% confidence intervals (CIs), and for continuous data, standard mean differences (SMDs) with 95% CI were used. In cases where the continuous outcome was reported in a study as median, range, and interquartile range, means and standard deviations were estimated using the formula described by Hozo et al. [21]. Heterogeneity was quantified in each analysis by the tau-squared and I^2 statistics. Values of $I^2 > 50\%$ and $> 75\%$ were considered to indicate moderate and significant heterogeneity among studies, respectively. A random-effects model was used to pool study results independently of the p-value for heterogeneity or I^2 [22].

Results

Characteristics of studies included in the meta-analysis

A total of 1,012 articles were identified from the Medline (PubMed), Embase, Cochrane library, and the manual search as described above. Ultimately, 19 studies [23–41] published from 2020 to 2021 which included 33,296 patients in the meta-analysis (Fig. 1). The details of the selected trials are summarized in Table 1.

Male gender in the AF/AFL and no-AF/AFL groups varied and amounted to 56.6% vs. 52.4% (OR: 1.23; 95% CI: 1.05–1.44; I^2: 64%; $p = 0.01$). Mean age of patients in AF/AFL group was 73.8 ± ± 11.2 years compared to 61.8 ± 17.5 years for no AF/AFL group (SMD: 0.90; 95% CI: 0.39–1.41; I^2: 99%; $p < 0.001$). Detailed characteristics of patient comorbidities are presented in the **Supplementary Table S1**.

Results of the meta-analysis

In-hospital mortality was reported in 18 studies and was 32.8% for AF/AFL group compared to 14.2% (RR: 2.18; 95% CI: 1.79–2.65; I^2: 90%; $p < 0.001$; Fig. 2). Sub-analysis showed that in-hospital mortality in new onset AF/AFL compared to the non-AF/AFL group amounted to 22.0% vs. 18.8% (RR: 1.86; 95% CI: 1.54–2.24; I^2: 72%; $p < 0.001$; Fig. 3).

In-hospital cardiovascular death was reported in 1 study [40] and was 10.4% vs. 5.2% respectively for patients with and without AF/AFL (RR: 2.02; 95% CI: 1.11–3.66; $p = 0.02$). Uribarri et al. [41] also showed 60-day mortality which was 43.3% vs. 30.9%, respectively (RR: 1.40; 95% CI: 1.10–1.79; $p = 0.02$).

Intensive care unit admission was required for 17.7% of patients with AF/AFL compared to 10.8% for patients without AF/AFL (RR: 1.94; 95% CI: 1.04–3.62; I^2: 72%; $p = 0.04$).

Mechanical ventilation was reported in 6 studies and was 14.4% vs. 5.2% for patients with and without AF/AFL (RR: 1.76; 95% CI: 0.92–3.36; I^2: 89%; $p = 0.09$).

A pooled analysis of the observed adverse events is presented in Table 2. Patients with AF/AFL had a higher risk of bleeding events (9.1% vs. 3.2%; RR: 3.50; 95% CI: 1.55–7.91; I^2: 47%; $p = 0.003$), heart failure (HF) (23.1% vs. 18.2%; RR: 1.39; 95% CI: 1.01–1.91; I^2: 35%; $p = 0.04$) as well as higher risk of acute kidney injury (AKI) (41.9% vs. 40.1%; RR: 1.31; 95% CI: 1.10–1.57; I^2: 0%; $p = 0.003$), compared to patients without AF/AFL.

Length of stay in ICU was reported in 2 studies and was 10.2 ± 21.9 days for AF/AFL group compared to 37.9 ± 18.7 days for no AF/AFL group (SMD: –1.40; 95% CI: –5.54 to 2.75; I^2: 100%; $p = 0.51$; Fig. 4).

Hospital length of stay in AF/AFL and no AF/AFL amounted to 9.4 ± 3.7 vs. 8.0 ± 3.1 days, respectively (SMD: 1.27; 95% CI: 0.18–2.36; I^2: 99%; $p = 0.02$).

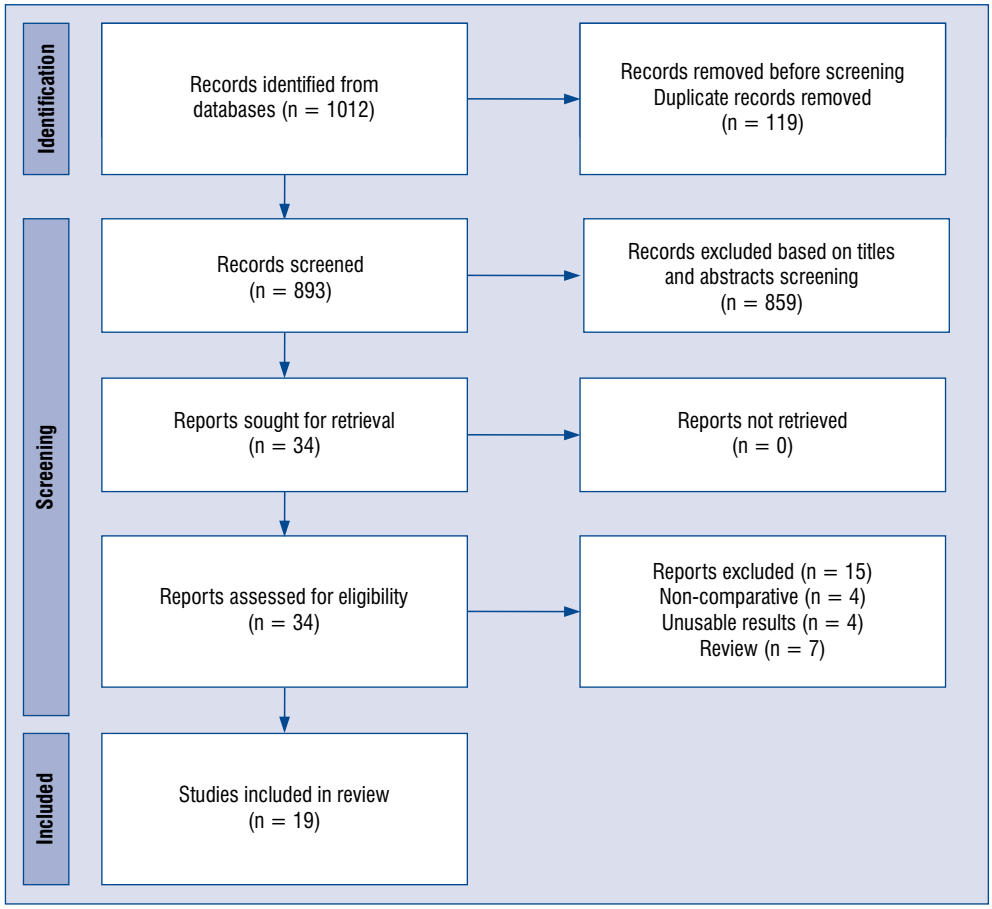

Figure 1. Flow diagram showing stages of the database search and study selection as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Discussion

General considerations and study population

Cardiovascular diseases, such as hypertension, have already been shown to worsen the prognosis of COVID-19 patients, both in terms of morbidity (increased risk of developing severe disease, need for hospitalization within ICU) and mortality [4, 8]. However, so far, no consensus has been reached regarding the impact of AF on the outcome of patients with COVID-19.

Atrial fibrillation and flutter are arrhythmias occurring mostly in the elderly, with hypertensive heart disease and coronary heart disease being the most frequently observed underlying disorders. According to previous studies, at least one risk factor, most often hypertension, is present among COVID-19 patients developing AF [42, 43]. However, there are also reports regarding new-onset AF emerging without any pre-existing illness [42, 44, 45]. The most prevalent comorbidities in patients with AF/AFL in this study included hypertension, chronic obstructive pulmonary disease (COPD) and CAD. Furthermore, the groups with AF/AFL tend to be of older age compared to groups without AF/AFL, with the difference in the mean age reaching as high as 24.6 years in one study [32].

Mortality in new-onset vs. pre-existing AF/AFL

Based on our findings, mortality was 2.18-fold higher in COVID-19 patients with pre-existing AF/AFL, compared to the non-AF/AFL group. This increase is much higher, compared to the previous meta-analysis, where the mortality was only 1.13--fold higher in patients with AF [17]. The reason for this difference, may be the inclusion of different populations in the present study, since the previous meta-analysis took into consideration only studies conducted in Europe and the United States. The magnitude of the increased risk in patients with pre-existing AF hospitalized due to COVID-19, remains to be established.

Table 1. Characteirsitcs of included trials.

Study	Country	Study design	Study group	No. of patients	Age, mean ± SD	Sex, male	Diabetes	Hypertension	CAD	LVEF, mean ± SD
Abdulrahman et al. 2021	Bahrain	Retrospective study	With AF Without AF	30 462	70.0 ± 11.8 52.3 ± 15.7	30 (100%) 462 (100%)	14 (46.7%) 166 (35.9%)	17 (56.7%) 181 (39.2%)	10 (33.3%) 49 (10.6%)	48.6 ± 11.7 51.2 ± 12.3
Denegri et al. 2021	Italy	Retrospective study	With AF Without AF	30 171	78.5 ± 12.6 66.8 ± 14.4	18 (60.0%) 111 (64.9%)	10 (33.3%) 27 (15.9%)	26 (86.7%) 88 (51.2%)	14 (46.7%) 21 (12.4%)	NS NS
Ergün et al. 2021	Turkey	Retrospective study	With AF Without AF	37 211	78.4 ± 3.6 69.5 ± 3	29 (78.4%) 147 (69.7%)	14 (37.8% 77 (36.5%)	31 (83.8%) 144 (68.2%)	11 (29.7%) 54 (25.6%)	NS NS
García-Granja et al. 2021	Spain	Retrospective study	With AF Without AF	54 463	81.6 ± 8.7 66.5 ± 14.9	35 (64.8%) 255 (55.1%)	13 (24.1%) 78 (16.4%)	40 (74.1%) 219 (47.3%)	NS NS	58.1 ± 11.7 62.6 ± 6.9
Harrison et al. 2020	UK	Retrospective study	With AF Without AF	6,589 6,589	73.6 ± 10.9 73.3 ± 10.9	3,587 (54.4%) 3,611 (54.8%)	2692 (40.9%) 2746 (41.7%)	5101 (77.4%) 5223 (79.3%)	3038 (46.1%) 3062 (46.5%)	NS NS
Iacopino et al. 2020	Italy	Retrospective study	With AF Without AF	12 18	75.9 ± 8.8 74.7 ± 10.2	10 (83.3%) 10 (55.6%)	5 (41.7%) 6 (33.3%)	12 (100.0%) 14 (77.8%)	NS NS	52.5 ± 5.8 55 ± 2.9
Ip et al. 2021	USA	Multicenter retrospective cohort study	With AF Without AF	60 111	74 63	NS NS	NS NS	NS NS	NS NS	NS NS
Kelesoglu et al. 2021	Turkey	Single-center prospectively study	With AF Without AF	33 625	72.42 ± 6.1 53.78 ± 13.8	16 (48.5%) 356 (57.0%)	7 (21.2%) 112 (17.9%)	22 (66.6%) 188 (30.0%)	NS NS	NS NS
Kelesoglu et al. 2021 (B)	Turkey	Single-center prospectively study	With AF Without AF	41 741	61.8 ± 6.1 55.5 ± 3.3	20 (48.8%) 418 (56.4%)	9 (22.0%) 121 (16.3%)	19 (46.3%) 226 (30.5%)	6 (14.6%) 107 (14.4%)	62.8 ± 1.4 63.3 ± 1.2
Lee et al. 2021	Republic of Korea	Retrospective study	With AF Without AF	130 7032	71.9 ± 13.7 47.3 ± 18.5	70 (53.9%) 2799 (39.1%)	46 (35.4%) 962 (13.7%)	98 (75.4%) 1511 (21.5%)	39 (30.0%) 232 (3.3%)	NS NS
Mountantonakis et al. 2021	USA	Retrospective study	With AF Without AF	1238 1238	73.1 ± 13.5 73.6 ± 13.3	777 (62.8%) 774 (62.5%)	547 (44.2%) 548 (44.3%)	925 (74.7%) 940 (75.9%)	584 (47.2%) 593 (47.9%)	NS NS
Musikantow et al. 2021	USA	Retrospective study	With AF Without AF	375 3595	76.8 ± 2.8 65 ± 3.7	225 (60.0%) 2063(57.4%)	125 (33.3%) 851 (23.7%)	208 (55.5%) 1159 (32.2%)	90 (24.0%) 320 (9.0%)	NS NS
Pardo Sanz et al. 2021	Spain	Retrospective study	With AF Without AF	12 148	75.9 ± 9.6 64.9 ± 16.3	8 (66.7%) 88 (59.5%)	3 (25.5%) 22 (14.9%)	9 (75.0%) 66 (44.6%)	NS NS	NS NS
Peltzer et al. 2020	USA	Retrospective study	With AF Without AF	166 887	74.5 ± 13.0 60.1 ± 17.0	120 (72.3%) 536 (60.4%)	50 (30.1%) 263 (29.7%)	114 (68.7%) 454 (51.2%)	45 (27.1%) 112 (12.6%)	59.4 ± 2.9 58.3 ± 2.8
Rubini-Costa et al. 2021	Spain	Retrospective study	With AF Without AF	151 151	74.6 ± 11.0 75.1 ± 12.0	82 (54.3%) 51 (53.6%)	46 (30.5%) 46 (30.5%)	115 (76.2%) 105 (69.5%)	NS NS	NS NS
Russo et al. 2021	Italy	Retrospective multicenter study	With AF Without AF	71 343	73.69 ± 9.9 65.54 ± 15.48	46 (64.8%) 207 (60.3%)	22 (31.0%) 84 (24.6%)	57 (80.3%) 206 (60.2%)	21 (29.6%) 45 (13.2%)	NS NS
Slipczuk et al. 2021	USA	Retrospective study	With AF Without AF	16 363	65.7 ± 4.1 67.5 ± 3	12 (75.0%) 171 (47.1%)	9 (56.3%) 218 (60.1%)	14 (87.5%) 254 (70.0%)	8 (50.0%) 143 (39.4%)	NS NS
Spinoni et al. 2021	Italy	Retrospective study	With AF Without AF	134 503	NS NS	NS NS	NS NS	NS NS	NS NS	NS NS
Urbarri et al. 2021	Spain	Retrospective study	With AF Without AF	233 233	79.7 ± 9.7 79.1 ± 11.5	134 (57.5%) 134 (57.5%)	69 (29.6%) 69 (29.6%)	189 (81.1%) 189 (81.1%)	NS NS	NS NS

AF — atrial fibrilation; CAD — coronary artery disease; LVEF — left ventricular ejection fraction; NS — not specified; SD — standard deviation; UK — United Kingdom; USA — United States of America

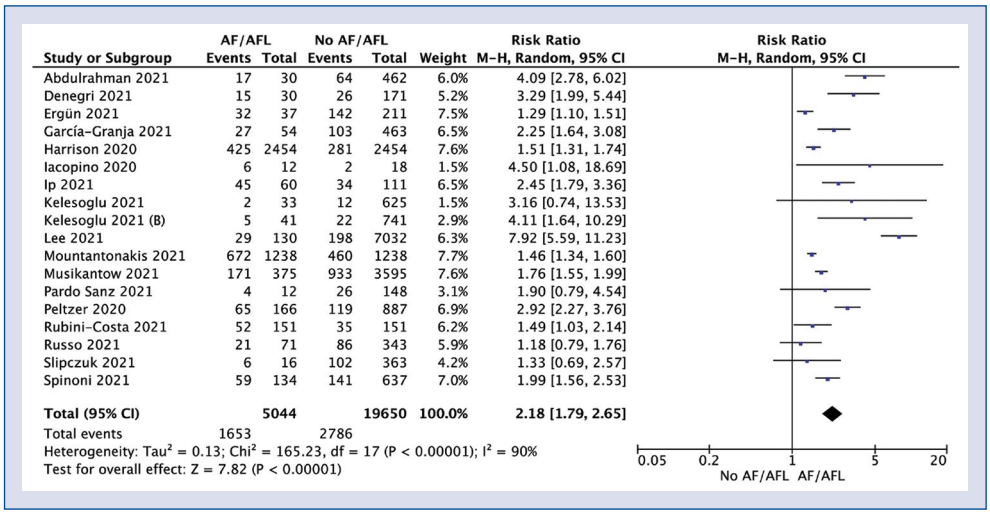

Figure 2. Forest plot of in-hospital mortality in atrial fibrillation/atrial flutter (AF/AFL) and no-AF/AFL groups. The center of each square represents the weighted risk ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

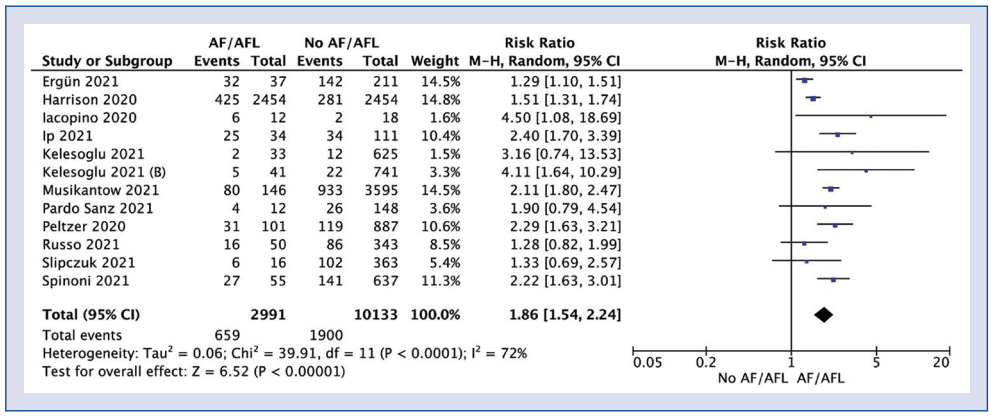

Figure 3. Forest plot of in-hospital mortality in new onset atrial fibrillation/atrial flutter (AF/AFL) no-AF/AFL groups. The center of each square represents the weighted risk ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results.

Due to a high prevalence of broad spectrum of comorbidities in patients with AF/AFL (e.g., hypertension, COPD, CAD) the distinction needs to be made between the impact of AF/AFL and the impact of other chronic diseases on in-hospital mortality. To date, in spite of the burden of comorbidities in patients with AF/AFL, many studies included in this meta-analysis confirmed that AF/AFL is an independent negative prognostic factor in patient with COVID-19 [23, 24, 29, 32, 33, 36, 37, 40, 41]. To confirm this finding, AF was associated with higher in-hospital mortality mainly in patients with a low or intermediate CHA_2DS_2-VASc score [15], suggesting that the existence of AF/AFL is not only the cumulative measure of risk due to other chronic diseases, but a novel prognostic factor. Hence, AF/AFL are potentially useful in clinical routine to identify patients at a higher risk of death, suggesting a need for a closer monitoring and a more intensive therapy.

Interestingly, the current study demonstrated that COVID-19 patients with new-onset AF/AFL had a 1.8-fold higher risk of mortality, compared to patients without AF/AFL, whereas patients with pre-existing AF had 2.18-fold higher risk of mortality, as compared to patients without AF/AFL. This suggests that especially pre-existing AF/AFL exerts its negative effects

Table 2. Polled analysis of adverse events among included trials.

Adverse event	No. of studies	Events/participants		Events		Heterogeneity between trials		P-value for differences across groups
		AF/AFL	No AF/AFL	RR	95% CI	P-value	I^2 statistic	
Embolic events	3	253/2699 (9.4%)	181/2835 (6.4%)	2.81	0.75–10.51	0.001	86%	0.12
APE	2	3/91 (3.3%)	14/674 (2.1%)	1.80	0.10–32.61	0.07	70%	0.69
Stroke	2	7/429 (1.6%)	34/4058 (0.8%)	1.95	0.87–4.37	0.75	0%	0.11
Bleeding events	4	41/450 (9.1%)	32/995 (3.2%)	3.50	1.55–7.91	0.13	47%	**0.003**
Acute MI	2	0/91 (0.0%)	11/674 (1.6%)	0.77	0.07–8.87	0.25	25%	0.84
Heart failure	3	75/324 (23.1%)	165/907 (18.2%)	1.39	1.01–1.91	0.22	35%	**0.04**
Myocarditis	2	0/66 (0.0%)	1/481 (0.2%)	2.81	0.12–68.19	NA	NA	0.53
Ventricular arrhythmia	1	1/54 (1.9%)	0/463 (0.0%)	25.31	1.04–613.72	NA	NA	0.05
CPR	1	1/37 (2.7%)	8/211 (3.8%)	0.71	0.09–5.53	NA	NA	0.75
Acute kidney injury	2	113/270 (41.9%)	178/444 (40.1%)	1.31	1.10–1.57	0.66	0%	**0.003**
RRT	1	14/37 (37.8%)	52/211 (24.6%)	1.54	0.95–2.47	NA	NA	**0.08**

AF — atrial fibrillation; AFL — atrial flutter; APE — acute pulmonary embolism; CI — confidence interval; CPR — cardiopulmonary resuscitation; MI — myocardial infarction; NA — not applicable; RR — risk ratio; RRT — renal replacement therapy

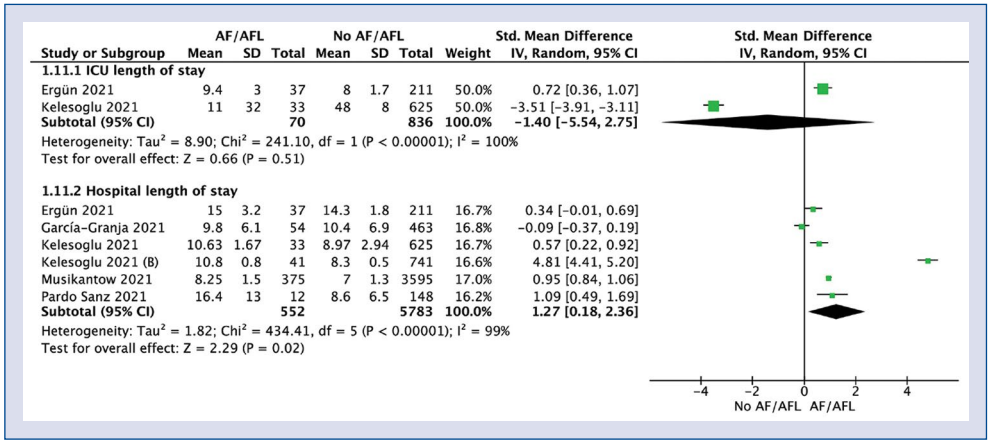

Figure 4. Forest plot of length of hospital stay in atrial fibrillation/atrial flutter (AF/AFL) and no-AF/AFL groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; ICU — intensive care unit.

in the course of COVID-19. The higher risk of mortality in the group with long-lasting AF/AFL can also be an indicator of a long-term hemodynamic compromise, caused by the persistent effect of arrhythmia on the effectivity of atrial systole, which may produce higher susceptibility for adverse outcomes.

Mid-term mortality

One study provided additional data on 60-day mortality, which indicated a slightly lower increase in mortality between the AF/AFL group, compared to the non-AF/AFL group (RR: 1.40) [41]. This may suggest that the highest burden of AF/AFL falls on the period

of first hospitalization, indicating the special need of intensive care and monitoring in the acute phase.

Reasons for increased mortality in AF/AFL

There are several theories explaining the association of AF/AFL with worse outcomes in COVID-19 that are strongly related to the molecular mechanisms underlying the electrical instability of atrial arrhythmias, hyperinflammatory state and mechanical stress on the cardiomyocytes.

Firstly, AF is associated with increased levels of angiotensin-converting enzyme 2 (ACE-2), the enzyme localized on the surface of coronary endothelial cells, cardiomyocytes and cardiac fibroblasts. In AF, levels of ACE-2 correlate strongly with the remodeling of the left atrium and play a pathophysiologic role by creating the substrate for arrhythmia [41, 46]. At the same time, ACE-2 is a receptor for SARS-CoV-2, allowing for viral entry. Higher levels of ACE-2 are associated with higher susceptibility for infections with SARS-CoV-2 and developing COVID-19 by allowing for a higher viral load within cells [46]. AF may be associated with higher levels of ACE-2, responsible for unfavorable outcomes. On the other hand, ACE-2 may also play a direct role in the cardiac involvement in the course of COVID-19. ACE-2 receptors are present on the cardiomyocytes as well pericytes in the vessels of microvasculature of the heart. Pericytes envelope the endothelial cells of microcirculation, providing vascular integrity [47–49]. It has been speculated that SARS-CoV-2 may interact with ACE-2 receptors on pericytes and lead to vascular leakage and consequent myocardial edema [11]. The edema, in turn, through increased interstitial hydrostatic pressure may lead to aberrations in ion channels conductance, predisposing patients with cardiac complications to AF. Consequently, a new-onset AF may be a manifestation of AKI.

Secondly, an inflammatory state underlies and predicts the onset of AF in humans [41]. An increasing body of evidence demonstrates the role of inflammatory markers (e.g., interleukin-6 and tumor necrosis factor alpha) [50–52], as well as inflammatory infiltrates within the myocardium in pathophysiology of AF [12, 53, 54]. Conversely, persistent AF itself favors remodeling by promoting inflammation, perpetuating the aberrations on the level of electrical conductance and producing the so-called 'AF begets AF' phenomenon. Consequently, individuals with long-lasting AF may be at higher risk of developing a hyperinflammatory reaction in the course of COVID-19 but also in patients undergoing COVID-19, developing a hyperinflammatory state, and are more likely to suffer from new-onset AF.

Thirdly, some studies suggest that AF may be the consequence of pulmonary vascular dysfunction (PVD), a condition frequently underlying acute respiratory distress syndrome. In this scenario, PVD is characterized by enhanced inflammatory signaling, remodeling and thrombosis within the microvasculature of the lungs, exerts mechanical stress on the right atrium and consequently on structural and electrical changes in cardiomyocytes. This creates a substrate for arrhythmias, especially AF. Studies conducted before the pandemic supported this hypothesis, showing a higher prevalence of AF in patients with pulmonary hypertension and tachycardia, both of which frequently occur in the course of COVID-19 [55]. In this regard, a new-onset AF would be a condition reflecting the occurrence of PVD.

Elucidating the exact cause or mechanism of death in individuals remains a challenge. This study demonstrated that in-hospital cardiovascular death occurred 2 times more often in the AF/AFL group compared to the non-AF/AFL group. These results are, however, based solely on one retrospective study, hence, does not allow drawing general conclusions. Therefore, we suggest that future studies should make the distinction between cardiovascular death, and non-cardiovascular causes. Also, due to the significance of inflammation in the pathophysiology of AF/AFL, we recommend measuring inflammatory parameters and correlating them with adverse outcomes.

ICU admission

The present study has demonstrated that ICU admission was required more frequently in the AF/AFL group compared to the non-AF/AFL group, although no significant difference in the ICU length of stay was observed. Further analysis of 2 studies [25, 30] provided insights regarding the mechanisms in which AF/AFL may contribute to worse outcomes in the examined group of patients. In the study of Ergün et al. [25], conducted with a group of ICU-patients, the laboratory findings showed an evident increase in the markers of cardiac injury (e.g., high sensitive troponin I; B-type natriuretic peptide) in the group with new-onset atrial fibrillation (NOAF) compared to the group without NOAF. Interestingly, no such difference was visible for C-reactive protein, white blood cell count, lymphocytes or neutrophils. In another study by Uribarri et al. [41] patients with AF have a significantly higher incidence of HF, but lower incidence of respiratory insufficiency, high

flow nasal cannula, both with noninvasive and invasive mechanical ventilation.

This suggests that AF/AFL may exert its detrimental effects (reflected by the necessity of therapy in ICU) through myocardial injury rather than only passively reflecting the lung pathology and hyperinflammatory state. These findings may be relevant for the therapy of COVID-19 patients, as the scenario where AF/AFL causes worse outcomes directly through cardiac injury that requires different specific therapy administered by a team with extensive cardiological knowledge, as compared to the scenario, where AF/AFL merely accompanies severe disease where the stress is put on anesthesiologic therapy.

Individual complications

The complications occur significantly more frequently in COVID-19 patients with AF/AFL, compared to those without AF/AFL including bleeding events, AKI and HF.

Bleeding complications occurred 3.5 times more often in the AF/AFL group compared to the non-AF/AFL group, based on 4 studies [26, 35, 37, 41]. Interestingly, 1 study reported that in patients with AF, a percentage of those treated with appropriate doses of anticoagulants was low (57%) [41]. The remaining individuals were either treated with a prophylactic dose only (25.7%) or did not receive any anticoagulant treatment (17.3%). In spite of that, the incidence of relevant bleeding complications in the AF group was more than 4 times higher compared to the non-AF group (OR: 4.03). The study by Rubini-Costa et al. [37] demonstrated no statistical association between any anticoagulant medication and the risk of major bleeding. Consequently, anticoagulants seem to be not the main factor responsible for bleeding and further research is warranted to investigate the pathophysiology behind bleeding complications.

The present study found that AKI is 1.31 higher in the patients with AF/AFL, as compared with patients without AF/AFL. In the study by Ergün et al. [25] in the NOAF group, compared with non-NOAF group, the incidence of secondary bacterial infections was higher (75.7% vs. 51.7%) and comparable to the frequency of AKI, suggesting that there may be links between these 2 phenomena and NOAF [25]. In fact, AF was described as the most common arrhythmia in patients with sepsis [56] and the one associated with increased mortality in this group [57], which demonstrates its links with the acute inflammatory state.

Conclusions

The present study showed that AF/AFL is associated with increased in-hospital mortality and worse outcomes in patients with COVID-19 and may be used as a negative prognostic factor in these patients. Patients with AF/AFL are at higher risk of hospitalization in ICU. The presence of AF/AFL in individuals with COVID-19 is associated with higher risk of complications, such as bleeding, AKI and HF. AF/AFL may be associated with unfavorable outcomes due to the hemodynamic compromise of cardiac function itself or hyperinflammatory state typical of these conditions.

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Conflict of interest: None declared

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Does left ventricular reverse remodeling influence long-term outcomes in patients with Chagas cardiomyopathy?

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Abstract

Background: *The impact of left ventricular reverse remodeling (LVRR) on the prognosis of Chagas cardiomyopathy is unknown. The aim of this study was to determine whether the presence of LVRR can predict mortality in these patients.*

Methods: *From January 2000 to December 2010, the medical charts of 159 patients were reviewed. LVRR was defined as an increase of left ventricular ejection fraction (LVEF) and a decrease of left ventricular end-diastolic diameter (LVDD) by two-dimensional echocardiography. No patient underwent cardiac resynchronization therapy or required mechanical ventricular assistance.*

Results: *At baseline, median (25^{th}–75^{th}) LVDD was 64 mm (59–70), and median LVEF was 33.2% (26.4–40.1). LVRR was detected in 24.5% of patients in a 40-month (26–64) median follow-up. In the LVRR group, LVDD decreased from 64 mm (59–68) to 60 mm (56–65; $p < 0.001$), and LVEF increased from 31.3% (24.1–39.0) to 42.5% (32.2–47.7; $p < 0.001$). However, LVRR was not associated with heart failure hospitalization, cardiogenic shock, heart transplantation, or mortality ($p > 0.05$ for all comparisons). The Cox proportional hazard model analysis identified only cardiogenic shock (hazard ratio [HR]: 2.41; 95% confidence interval [CI]: 1.51–3.85; $p < 0.001$) and serum sodium level (HR: 0.91; 95% CI: 0.86–0.96; $p < 0.001$) as independent predictors of all-cause mortality.*

Conclusions: *Left ventricular reverse remodeling occurs in one quarter of patients with Chagas cardiomyopathy and have no impact on the outcomes of patients with this condition.* (Cardiol J 2022; 29, 1: 44–52)

Key words: left ventricular remodeling, heart failure, Chagas cardiomyopathy, prognosis; mortality

Introduction

In the current era, Chagas disease is still a major health problem in Latin America, where about 10 million individuals are carriers of the disease, and about 10,000 people die as result of the disease each year [1]. In view of international immigration, Chagas disease has spread throughout the world, and the global costs associated with this disease are about 7.2 billion United States Dollars annually, this is higher than that observed in several types of cancer [2].

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The disease is caused by *Trypanosoma cruzi*, a protozoan transmitted to humans through the feces of a sucking bug. Infection usually occurs in infancy. Approximately two decades after infection, about 30% of infected patients develop chronic cardiomyopathy and severe complications, as chronic systolic heart failure, and sudden cardiac death [3].

Chronic heart failure (CHF) secondary to Chagas cardiomyopathy (CC), CC has a poor prognosis compared to patients with ischemic cardiomyopathy [4], hypertensive cardiomyopathy [5], or idiopathic dilated cardiomyopathy [6, 7]. The histopathological findings in the chronic stage of CC are focal myocarditis that leads to myocyte loss, reparative, and confluent fibrosis throughout the myocardium, ultimately leading to geometric changes and ventricular systolic dysfunction i.e., ventricular remodeling [8].

Left ventricular reverse remodeling (LVRR) is characterized by a decrease of left ventricular (LV) dimensions, normalization of LV shape and improvement of systolic function [9]. A favorable response to drug therapy with angiotensin converting enzyme inhibitors, beta-blockers and aldosterone antagonists has been reported, with almost complete reversal of LV dysfunction [10–12]. Although Chagas heart disease has been extensive and intensively studied over the past 20 years, a limited number of studies have assessed cardiac remodeling quantitatively in long-term follow-up in this setting [13, 14]. Male gender and systemic blood pressure seem to be independent predictors of cardiac remodeling [15].

The ability of treatment for heart failure to decrease left chamber size and to improve left ventricular ejection fraction (LVEF) can identify CC patients with a modifiable condition and better long-term prognosis. Accordingly, the aim of this study was to determine whether LVRR could predict all-cause mortality in patients with CC in long-term follow up.

Methods

Patients selection

This single-center study retrospectively evaluated the medical charts of patients with two positive serologic tests for Chagas disease (hemagglutination and indirect immunofluorescence staining) according to the World Health Organization recommendation [16]. The clinical diagnosis of heart failure was made by attending physicians based on Framingham Criteria for the diagnosis of CHF [17]. After the clinical diagnosis of CHF, a two-dimensional (2D) echocardiography was used for each patient to confirm the clinical diagnosis, quantify this condition using LVEF, and to guide treatment. Individuals with the clinical diagnosis of CHF, secondary to CC and LVEF < 55% on first 2D echocardiography confirming LV systolic dysfunction were initially screened for this study. Patients with a concomitant disease that could potentially cause heart disease by itself were excluded.

This study was conducted in accordance with the Declaration of Helsinki and approved through the local Human Research Ethics Committee of São José do Rio Preto Medical School (CAAE — 02716112.6.0000.5415). The need for individual informed consent was waived, as this study was a retrospective analysis of prospectively collected data for routine care, and breach of privacy or anonymity did not occur.

Data availability

The data sets generated and/or analyzed during the current study are not publicly available due to the use of potentially identifying postal codes in the deprivation analysis, as approved by the local Human Research Ethics Committee, but they are available upon reasonable request.

Baseline measurements and 2D echocardiographic conditions

The demographics data, New York Heart Association (NYHA) functional class, heart rate, systemic arterial pressure, medical history, standard laboratory tests, 12-lead resting electrocardiogram and cardiac electronic implantable devices information were obtained upon study entry and retrieved from the medical chart records.

Local specialists in 2D echocardiography did the echocardiographic examination with patients in the left lateral position. Standard parasternal, apical and subcostal views were obtained. Routinely, physicians did place the transducer as far laterally and caudally as possible in the apical windows to maximize LV cavity size and avoid foreshortening during measures. LVEF was measured by the Simpson method in the apical 4-chamber view, which was used for the main analyses, as well as apical 2-chamber view when possible. Wall motion abnormalities analyses, LV end-systolic diameter, LV end-diastolic diameter (LVDD), and right ventricular dimension were measured according to the American Society of Echocardiography recommendations [18].

Although there is lack of standardized definitions for reverse remodeling [19], in the present

investigation, LVRR is defined by the simultaneous presence of the following conditions: a) occurrence of an increase of LVEF concomitant with a decrease in LVDD; b) this improvement occurred in the absence of cardiac resynchronization therapy or mechanical ventricular assistance, as also described by Amorim et al. [9]. At the time of the study period, LV volumes were not routinely measured.

Prospective follow-up

The patients were routinely followed from January 02, 2000 to December 30, 2010 at the Cardiomyopathy Outpatient Service, Hospital de Base, São José do Rio Preto Medical School, a public referral center for severe CHF management in the northwest of São Paulo, Brazil. The heart failure medical therapy information was retrieved from a prospectively collected database of patients. All patients received evidence-based treatment for CHF, according to international guidelines at that time. Thus, treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blocks and beta-blockers at targeted or maximal tolerated doses was considered for all patients. Those with pitting edema received furosemide, while those in the NYHA class III/IV with a LVEF < 30% were treated with digoxin. Patients usually visited the outpatient service every 4 months, and a senior heart failure specialist supervised the treatment given. Patients were followed until the study was closed; they were also excluded at heart transplantation or death.

Data analysis

Data were analyzed using the IBM SPSS Statistical Package v.21 (IBM Corporation, Armonk, NY). Variables are presented as absolute numbers and percentages and median and interquartile ranges (25^{th} and 75^{th} percentile) when applicable. Due to the lack of Gaussian distribution, continuous variables were compared using the nonparametric Mann-Whitney test. Chi-square or the Fisher exact test was used to compare categorical variables.

The Cox proportional hazards model was used to evaluate the ability of LVRR to independently predict all-cause mortality during long-term follow-up. In the multivariable model, variables with a p value < 0.10 in the univariate model, and those with known prognostic significance were entered into the backward stepwise approach to establish independent predictors of death. The Spearman test was used to establish a correlation between continuous variables. The variable which correlated with others and with the highest Wald coefficient remained in the model, whereas the other was ruled out. Thus, each variable entered the multivariable model in a proportion of at least 10 events in an attempt to avoid overfitting. The adjusted hazard ratio (HR) and 95% confidence intervals (95% CI) were calculated for predictors.

Cumulative survival graphics (Kaplan-Meier) were constructed to demonstrate differences in event-free survival (mortality from all-causes). P values < 0.05 were considered statistically significant (two-tailed).

Results

Potentially 234 patients were screened for taking part in this investigation. However, a total of 75 (32%) individuals did not undergo another comparative 2D echocardiography during the follow-up because they had died before this. Therefore, they were excluded from this investigation. In this context, the study evaluated 159 patients (64.2% male) who had a median age of 57 (47–66) years, and were followed over a period more than 10 years. The baseline characteristics of the patients are shown in Table 1. These individuals were divided into two groups: with and without LVRR by echocardiographic evaluations. A similarity (p > 0.05) for all variables was observed in the present series.

The current study population received maximal tolerated daily doses of medications, considering samples from drug classes with known prognostic impact in ventricular remodeling. LVRR group received mean daily dose (mg/day) of enalapril (15.0 ± 5.8), captopril (106.3 ± 49.6), losartan (44.2 ± 11.0), carvedilol (27.6 ± 21.1), metoprolol succinate (116.7 ± 58.7), spironolactone (33.3 ± ± 24.3) and non-LVRR group received mean daily dose of enalapril (14.3 ± 8.7; p = 0.357), captopril (75.8 ± 38.0; p = 0.120), losartan (50.0 ± 24.2; p = 0.789), carvedilol (26.3 ± 17.9; p = 0.860), metoprolol succinate (128.1 ± 63.6; p = 0.585), spironolactone (27.5 ± 12.4; p = 0.346), showing no difference between groups for optimized therapy, according to guideline recommendations during the long-term follow-up.

Thirty-nine patients (24.5%) with CC presented LVRR during their follow-up. Comparing the first and the last 2D echocardiography, this group showed a median of 3.0 mm (1 to 6 mm) for absolute reduction of LVDD, representing a median of 5.1% (1.7 to 10%) reduction. For this group, a median of absolute improvement for LVEF of 7.0% (4.0 to 11.6%) was also detected, representing around

Table 1. Baseline characteristics of 159 patients analyzed for occurrence of left ventricular reverse remodeling (LVRR).

Baseline characteristics	All patients (n = 159)	LVRR+ (n = 39)	LVRR– (n = 120)	P
Variable:				
Age [years]	57 (47–66)	58 (52–67)	56 (45–65)	0.159
Gender (male)	102 (64.2)	23 (59.0)	79 (65.8)	0.438
NYHA classes I and II	118 (74.2)	33 (84.6)	85 (70.8)	0.087
NYHA classes III and IV	41 (25.8)	6 (15.4)	35 (29.2)	0.087
Heart rate [beats/min]	68 (60–78)	68 (60–80)	68 (60–76)	0.681
SBP [mmHg]	110 (100–120)	110 (100–120)	110 (100–120)	0.687
DBP [mmHg]	70 (60–80)	70 (70–80)	70 (60–80)	0.136
Diabetes mellitus	4 (2.5)	2 (5.1)	2 (1.7)	0.252
Laboratory analysis:				
Hemoglobin [g/dL]	13.2 (12.0–14.0)	13.8 (12.0–14.1)	13.2 (12.0 -14.0)	0.877
Sodium [mg/dL]	141 (138–144)	141 (137–144)	141 (138–144)	0.794
Potassium [mg/dL]	4.4 (4.1–4.8)	4.4 (3.9–4.8)	4.4 (4.1–4.8)	0.869
Creatinine [mg/dL]	1.2 (1.0–1.4)	1.1 (1.0–1.3)	1.2 (1.0–1.4)	0.157
CKD-EPI [mL/min/1.73 m^2]	63.5 (51.1–78.6)	65.3 (52.2–78.6)	63.3 (50.6–79.2)	0.658
Electrocardiography:				
Atrial fibrillation	41 (25.8)	12 (30.8)	29 (24.2)	0.413
ICD	23 (14.5)	6 (15.4)	17 (14.2)	0.851
Pacemaker	84 (52.8)	18 (46.2)	66 (55.0)	0.336
LBBB	21 (13.2)	3 (7.7)	18 (15.0)	0.242
RBBB	63 (39.6)	16 (41.0)	47 (39.2)	0.837
LAFB	59 (37.1)	15 (38.5)	44 (36.7)	0.840
Low voltage of QRS	9 (5.7)	1 (2.6)	8 (6.7)	0.455
VPC	71 (44.7)	19 (48.7)	52 (43.3)	0.557

Data are shown as median (25^{th}–75^{th}) or number (%). N — number of individuals; NYHA — New York Heart Association functional class; SBP — systolic blood pressure; DBP — diastolic blood pressure; CKD-EPI — estimated glomerular filtration rate according Chronic Kidney Disease Epidemiology Collaboration; ICD — implantable cardioverter-defibrillator; LBBB — left bundle branch block; RBBB — right bundle branch block; LAFB — left anterior fascicular block; VPC — ventricular premature contraction

23.6% (12.7 to 39.7%) of improvement. There was a significant difference between this group and the group of individuals with LVRR ($p < 0.001$) for all previous measures. Right ventricle diameter and wall motion abnormality did not differ between groups (Table 2).

Standard laboratory tests, 12-lead resting electrocardiographic findings and using cardiac electronic implantable devices observed at study entry were not associated with LVRR occurrence. Moreover, patients with LVRR showed no difference for hospitalization due to acute decompensated heart failure (59.0%), cardiogenic shock (17.9%), and the need to heart transplantation (10.3%) compared to patients without LVRR (65.8%, $p = 0.438$; 29.2%, $p = 0.167$; and 8.3%, $p = 0.747$; respectively).

The Cox proportional hazards model showed a similar situation for late-mortality (over period of more than 10 years) between individuals without LVRR (54.2%) compared to individuals with LVRR (46.2%, $p = 0.384$). After adjustment, six variables were used in the multivariate model: age (years), gender (male), cardiogenic shock, left anterior fascicular block, serum sodium level, and LVRR. Only two variables were retained as independent predictors of long-term mortality: cardiogenic shock (hazard ratio [HR]: 2.41, 95% CI 1.51–3.85; $p < 0.001$) and serum sodium level (HR: 0.91, 95% CI 0.86–0.96; $p < 0.001$; Table 3).

The Kaplan-Meier survival analysis of patients with and without LVRR during follow-up is shown in Figure 1. No difference between either group was observed regarding survival.

Table 2. Comparison between first and last two-dimensional-echocardiography (2D-ECHO) during follow-up.

Baseline characteristics	All patients (n = 159)	LVRR+ (n = 39)	LVRR– (n = 120)	P
First 2D-ECHO:				
LVDD [mm]	64 (59–70)	64 (59–68)	64 (59–71)	0.605
LVSD [mm]	54 (49–60)	56 (50–60)	54 (48–60)	0.440
RVD [mm]	23 (19–28)	24 (20–29)	23 (18–28)	0.272
WMA	54 (34.0)	12 (30.8)	42 (35.0)	0.628
LVEF [%]	33.2 (26.4–40.1)	31.3 (24.1–39.0)	33.5 (27.0–40.8)	0.223
Last 2D-ECHO:				
LVDD [mm]	65 (60–72)	60 (56–65)	67 (62–74)	< 0.001
LVSD [mm]	56 (49–63)	49 (42–55)	58 (52–64)	< 0.001
RVD [mm]	25 (20–33)	27 (22–35)	25 (19–32)	0.485
WMA	50 (31.4)	11 (28.2)	39 (32.5)	0.616
LVEF [%]	31.7 (24.8–41.8)	42.2 (32.2–47.7)	30.0 (22.7–36.7)	< 0.001
Comparison LVDD:				
Absolute difference [mm]	1.0 (–1.0 to 4.0)	–3.0 (-6.0 to–1.0)	2.0 (0.0 to 5.0)	< 0.001
Relative difference [%]	1.4 (–1.8 to 6.0)	–5.1 (–10.0 to –1.7)	3.2 (0.0 to 8.1)	< 0.001
Comparison LVEF:				
Absolute difference [mm]	0 (–7.8 to 6.4)	7.0 (4.0 to 11.6)	–3.1 (–10.6 to 3.2)	< 0.001
Relative difference [mm]	0 (–23.3 to 23.6)	23.6 (12.7 to 39.7)	–8.4 (–28.8 to 12.0)	< 0.001

Data are shown as median (25^{th}–75^{th}) or number (%). LVRR — left ventricular reverse remodeling; N — number of individuals; LVDD — left ventricular end-diastolic diameter; LVSD — left ventricular end-systolic diameter; RVD — right ventricular diameter; WMA — wall motion abnormalities; LVEF — left ventricular ejection fraction

Table 3. Cox proportional hazard model for independent predictors of long-term mortality.

All patients	Univariate			Multivariate		
	HR	95% CI	P	HR	95% CI	P
Age [years]	1.00	0.98–1.01	0.688			
Gender (male)	1.43	0.89–2.30	0.142			
LVRR status	0.76	0.45–1.28	0.303			
Cardiogenic shock	2.49	1.58–3.91	< 0.001	2.41	1.51–3.85	< 0.001
Left anterior fascicular block	1.72	1.12–2.65	0.014			
Serum sodium level	0.91	0.86–0.96	0.001	0.91	0.86–0.96	< 0.001

HR — hazard ratio; CI — confidence interval; LVRR — left ventricular reverse remodeling

Discussion

In this study, LVRR in CC was evaluated as a predictor of long-term mortality. According to available research, this is the first study of a cohort of patients with CHF secondary to CC evaluating the role of LVRR on outcome in an over 10-year follow-up. The present study shows no survival improvement despite of LVRR, thus confirming a dismal prognosis and severity of CHF secondary to CC.

Cardiac reverse remodeling with medical treatment of CHF is well established, with demonstrable decreases in LV diameter and improvement in LV function [20–25]. It should be noted that, although the volumetric measurements seem to provide the most powerful data, LVEF measurements are simpler to obtain and are indeed a marker of the remodeling process. As LV volume increases, there is a tendency for a concomitant and usually parallel decrease in LVEF, which can be used,

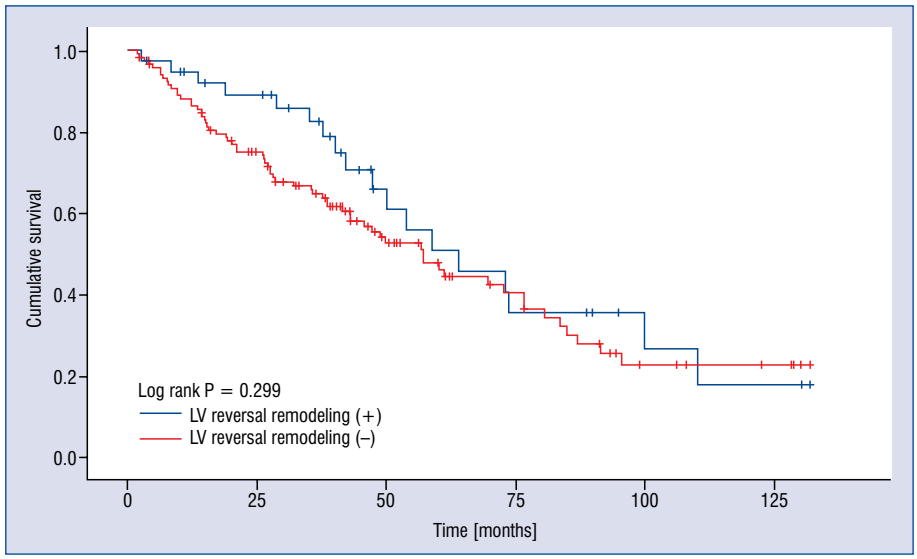

Figure 1. Kaplan-Meier survival analysis of patients with and without left ventricular (LV) reverse remodeling considering reduction of left ventricular end-diastolic diameter and improvement of left ventricular ejection fraction.

itself, as a marker of the remodeling process [26]. Interestingly, similar to the results provided by Ramasubbu et al. [27] using the echocardiography database from the ESCAPE trial [28], the current study demonstrated that changes in these parameters were not associated with outcome improvement (long-term mortality) in patients with CC as well. In this context, despite LVRR evidenced by improvement in cardiac chamber size and LV function, factors as persistent neurohormonal activation, increased oxidative stress, and inflammatory/immunological cardiomyocyte damage can be a potential hypothesis to explain the present findings [19, 29].

Only two previous studies which included patients with CC aiming at assessing clinical predictors for long-term cardiac remodeling was previously performed in a similar cohort. In both studies [13, 15], in contrast to the present results, no significant reduction for LVDD was observed during follow-up. It is possible that optimized clinical treatment provided to patients in the current study, including targeted or maximal tolerated doses of angiotensin converting enzyme inhibitors and spironolactone associated to beta-blockers, can account for these discrepant results. Moreover, findings herein are similar to those observed in other populations [30, 31].

The therapeutic agents, mainly angiotensin converting enzyme inhibitors and beta-blockers, modify the remodeling process and frequently add other clinically relevant benefits in reducing morbidity and mortality in cardiomyopathy patients [32]. Several clinical trials using a variety of beta-blockers have demonstrated improvements in symptoms, ventricular function, functional capacity, and survival in patients with CHF due to ischemic and dilated cardiomyopathies [33–35]. Some studies with beta-blockers that included patients with CC showed similar benefits [36–40].

Experimentally, a recent study designed to evaluate the role of carvedilol in the context of Chagas disease concluded that the drug did not attenuate cardiac remodeling or mortality in a model of CC [41]. This contrasts with other experimental studies in which metoprolol was capable in reverting electrocardiographic abnormalities in a rat model of Chagas disease, was probably because the reversal of catecholamine toxicity in this model [42, 43]. In fact, parasympathetic derangement is believed, along with microvascular dysfunction and autoimmunity, to play a central role in the pathogenesis of chronic Chagas heart disease [44]. Thus, in the present study, optimized pharmacological treatment confirmed its association with LVRR, considering the reduction of LVDD and improvement of LVEF, although it has not positively impacted on survival.

Inotropic support and serum sodium level were independent predictors for mortality in the current investigation. These findings probably reflect the severity of the study population in which about a quarter of individuals showed cardiogenic shock during follow-up. Therefore,

this may account, at least in part, for the ability of inotropic support to predict hyponatremia in patients with CC and, consequently, ventricular remodeling [45, 46].

Limitations of the study

There are some limitations to the present study. This work is a retrospective analysis of prospectively collected single-center data and thus, carries the inherent disadvantages of retrospective studies. All echocardiographic parameters were not available in all patients, and therefore only parameters that had paired measurements (at baseline and follow-up) were used in the analysis, resulting in a smaller sample size. Unfortunately, LV volumes were not obtained, a finding that could better explain LVRR. It must be emphasized that 32% of patients were excluded from the study because they had died before undergoing comparative echocardiography. This reflects the mortality associated with Chagas disease patients in the real world. Intra- and interobserver variability for the echocardiography lab was not mentioned; therefore, it was difficult to determine whether the mean changes in parameters fell within the measurement variability or reflected true changes. Additionally, multivariate analysis included only those factors available in the documented database. Some factors that have an effect on prognosis might not have been examined. Thus, present results may not be applicable to other specific patient cohorts without further study into the various subgroups. Despite these caveats, it should be emphasized that this study was performed in a cohort followed at a tertiary referral center for heart failure treatment, where patients received the best therapy possible. In addition, the data obtained allowed us to perform an ample statistical analysis, which provided its great reliability. Finally, the investigation reflects the relentless prognosis of CC in the real world, independent of LVRR.

Conclusions

The present study suggests that LVRR does not predict a reduction in long-term all-cause mortality in patients with CC. This is the first study to show that the severity of disease progression seems to dissipate the potential benefit of LVRR in patients with CC. Further research, however, with larger sample sizes, should be conducted to confirm these findings.

Conflict of interest: None declared

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Filter life span in postoperative cardiovascular surgery patients requiring continuous renal replacement therapy, using a postdilution regional citrate anticoagulation continuous hemofiltration circuit

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Abstract

Background: *Regional citrate anticoagulation (RCA) is the recommended standard for continuous renal replacement therapy (CRRT). This study assesses its efficacy in patients admitted to critical care following cardiovascular surgery and the influence of standard antithrombotic agents routinely used in this specific group.*

Methods: *Consecutive cardiovascular surgery patients treated with postdilution hemofiltration with RCA were included in this prospective observational study. The primary outcome of the study was CRRT circuit life-span adjusted for reasons other than clotting. The secondary outcome evaluated the influence of standard antithrombotic agents (acetylsalicylic acid [ASA], low molecular weight heparin [LMWH] or fondaparinux as thromboprophylaxis or treatment dose with or without ASA) on filter life.*

Results: *Fifty-two patients underwent 193 sessions of continous veno-venous hemofiltration, after exclusion of 15 sessions where unfractionated heparin was administered. The median filter life span was 58 hours. Filter life span was significantly longer in patients receiving therapeutic dose of LMWH or fondaparinux (79 h [2–110]), in comparison to patients treated with prophylactic dose of LMWH or fondaparinux (51 h [7–117], $p < 0.001$), and patients without antithrombotic prophylaxis (42 h [2–91], $p < 0.0001$). 12 bleeding episodes were observed; 8 occurred in patients receiving treatment dose anticoagulation, 3 in patients receiving prophylactic dose anticoagulation and 1 in a patient with no antithrombotic prophylaxis.*

Conclusions: *A postdilution hemofiltration with RCA provides prolonged filter life span when adjusted for reasons other than clotting. Patients receiving treatment dose anticoagulation had a significantly longer filter life span than those who were on prophylactic doses or ASA alone.* (Cardiol J 2022; 29, 1: 53–61)

Key words: cardiovascular surgical procedures, continuous renal replacement therapy, hemofiltration, anticoagulants, citric acid

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Introduction

Acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) after cardiac surgery affects between 2% and 5% of patients and carries a mortality rate between 36% and 78% [1, 2]. Regional citrate anticoagulation (RCA) is the Kidney Disease-Improving Global Outcome (KDIGO) recommended anticoagulation of choice for CRRT and is of particular value to patients with contraindications to heparin and high risk of bleeding such as those who have undergone cardiac surgery [3, 4]. RCA is also associated with a prolonged filter life-span due to a decreased incidence of clotting and preservation of the filter sieving coefficient for larger molecules including inflammatory mediators [5, 6]. This anticoagulation modality was reported to be safe and preferred after cardiac surgery [7].

Therefore, although RCA is commonly used in continuous veno-venous hemodialysis (CVVHD) and hemodiafiltration (CVVHDF) modes as these potentially offer reduced risk of clotting over purely convective modes, continuous veno-venous hemofiltration (CVVH) with RCA on a high cut-off membrane may be of specific benefit to this group of patients provided filter life span remains long [8, 9]. The Nikkiso Aquarius CRRT platform has been proven to be simple, effective and safe in delivering RCA for a postdilution CVVH method with a calcium containing replacement fluid in a general critical care population [10].

Cardiac surgery patients often need postoperative antithrombotic prophylaxis but the type and dose varies. Most coronary surgery patients require antiplatelet therapy, while patients after valve surgery can be treated with bridge antithrombotic prophylaxis with unfractionated heparin (UFH) or low molecular weight heparin (LMWH), until they can reach therapeutic international normalized ratio (INR) values resulting from oral anticoagulants administration though routine use remains open for debate [11].

As RCA has been reported to improve filter survival in patients receiving systemic anticoagulation with UFH for indications other than CRRT, e.g. patients on veno-arterial extracorporeal membrane oxygenation, it is the default anticoagulation method for CRRT in post cardiac surgery patients, in the absence of contraindications to citrate [12].

This study aims to evaluate the effect of postdilution CVVH with RCA anticoagulation on filter life span in general in this specific group of patients, and whether routine thromboprophylaxis adds additional benefit.

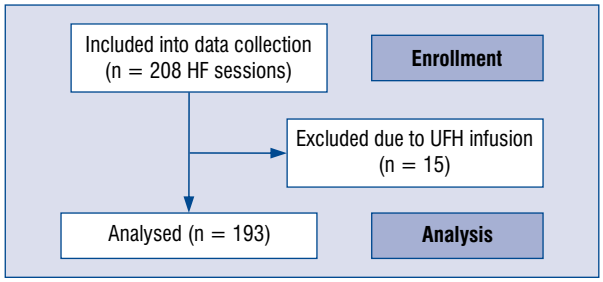

Figure 1. The flow-chart of hemofiltration sessions included into continuous renal replacement therapy circuit lifespan analysis; HF — heart failure; UFH — unfractionated heparin.

Methods

The study protocol conformed to the Ethical Principles for Medical Research Involving Human Subjects outlined in the Declaration of Helsinki, was approved by the local institutional review board for scientific studies (NKBBN/539/2016-17) and is registered in the Clinical Trials database (NCT03836742). Consecutive cardiovascular surgery patients treated with CVVH RCA between September 2015 and November 2017 were included (Fig. 1).

The decision to initiate renal replacement therapy was made by the treating clinician based on clinical features of volume overload and biochemical features of azotemia [3]. Contraindications to RCA were severe chronic liver disease, acute liver injury with INR > 2 and refractory shock with lactate increasing above 8 mmol/L.

Hemofiltration and RCA protocol

Continuous veno-venous hemofiltration was performed with the Aquarius+ CRRT machine with version 6.02.14/15 software (Aquarius system, NIKKISO Europe GmbH, Desbrocksriede 1, 30855 Langenhagen, Germany) and CITRASET RCA for therapies with regional citrate anticoagulation comprising Aqualine RCA (Haemotronic S.p.A, Via Carreri 16, 41037 Mirandola, Italy) and AQUAMAX hemofilter (Nikkiso Belgium bvba, Industriepark 6, 3300 Tienen, Belgium). Filter size (either Aquamax 1.2 m^2 or Aquamax 1.9 m^2) was determined by the treating clinician and depended on the patient's actual body weight (> 90 kg) and or the presence of distributive shock requiring noradrenalin infusion over 0.1 μg/kg/h, where an Aquamax 19 was used. In all patients Accusol 35 K0 (Nikkiso, Belgium Industriepark 6 B-3300 Tienen; Belgium), which contains 1.75 mmol/L of Calcium, was used as

the postdilution replacement fluid. Anticoagulant citrate dextrose solution A, U.S.P. (ACD-A) (ACD-A, Macopharma, 5003F Rue Lorthiois, 59420 Mouvaux, France) was used as the source of citrate.

Three thousand units of UFH were added to 1 L 0.9% NaCl solution for CRRT circuit priming in all but 7 patients who had a suspicion of heparin induced thrombocytopenia (HIT).

Initial settings of hemofiltration parameters and its modifications when metabolic alkalosis was observed, were adopted from the CVVH RCA protocol published by Kirwan et al. [10], however the renal dose was calculated for the actual body weight.

The plasma concentration of ionized calcium (iCa) was augmented with additional calcium supplementation initially using a dose of 10 mL of 10% Calcium Chloride (WZF Polfa, Karolkowa Str. 22/24, Warsaw, Poland) added to 1 L of normal saline which resulted in Ca^{++} concentration of 4.6 mmol/L. Due to low ionized calcium plasma concentration, after the first 10 patients its dose was increased to 20 mL 10% calcium chloride, and after the following 10 patients to 40 mL 10% calcium chloride, equivalent to Ca^{++} concentration of 18.4 mmol/L. The target calcium concentration in plasma was increased from the original 0.9–1.2 range to a 1.0–1.2 range. Similarly, the original protocol was modified by an additional routine infusion of 0.2 g/h magnesium sulfate.

Blood flow was set to achieve a filtration ratio of ~20%. If the plasma pH increased above 7.5 or bicarbonate concentration above 40 mmol/L the hemofiltration dose was decreased from the initial 35 mL/kg/h to 25 mL/kg/h. If metabolic alkalosis persisted, the citrate dose was reduced and if this did not resolve the issue within 3 h RCA was stopped [10].

Either 13.5 Fr Mahurkar catheters (Covidien, 15 Hampshire Str., Mansfield, MA 02048USA) or 12 Fr Hemo-Access (Biometrix Ltd., 4 Kiryat Mada, Jerusalem, Israel) with length depending on cannulation site were used, however the type of the catheter was not reported in patients' files.

Primary endpoint of this study was to assess filter lifespan in postdilution CVVH with RCA in cardiovascular surgery patients. Secondary endpoint evaluated the difference in filter life span depending on standard antithrombotic agents by separating hemofiltration sessions into three groups; Group A: no antithrombotic medication or acetylsalicylic acid (ASA) alone; Group B: prophylactic dose LMWH or fondaparinux, with or without ASA; Group C: treatment dose LMWH or fondaparinux with or without ASA. Fondaparinux was used instead of LMWH whenever HIT was suspected and HIT ELISA test was positive [13].

Treatment sessions where continuous UFH added for therapeutic reasons were excluded from filter survival analysis.

Statistical analysis

Data are presented as median, quartiles and ranges. CRRT circuit lifespan is presented as Kaplan-Meier curves. Categorical variables were compared between groups with the χ^2 test. Intergroup differences in filter lifespan were assessed with the Cox-Mantel test.

Results

Two hundred and eight CVVH sessions were performed in 52 patients (including 4 chronic dialysis patients). Fifteen sessions were excluded as the patients received an additional UFH infusion. Patients characteristics and cardio-vascular surgical procedures are presented in Table 1.

Primary endpoint

Filter life span of 193 sessions was adjusted for reasons to stop the filter other than clotting (96) and these included patient death (3), clinical decision (14), transport to computed tomography scan (2), change of therapy (2), technical (3: 1 alkalosis, 1 machine failure, 1 access concern) and end of filter life span (73).

Median time CRRT circuit lifespan was 58 h (2–117). CRRT circuit lifespan reached the 72-h manufacturer cut off in 75 (38.9%) sessions (Fig. 2).

Secondary endpoint

A significantly longer filter life span was observed in RCA CVVH sessions when patients received a treatment dose LMWH or fondaparinux (Table 2, Fig. 3).

Bleeding complications were observed in 12 patients (23%) (6 major) during or after CRRT and are presented in Table 3. Nine patients with bleeding complications were treated with treatment dose LMWH or fondaparinux, one with UFH, one with prophylactic dose LMWH and one with ASA alone (NS).

Discussion

According to available research, this is the first study of postdilution CVVH with RCA antico-

Table 1. Patient characteristics and type of surgical procedures in the study group.

Patient characteristics/type of surgery	Data/number of patients
Patients age	70 (Q_1 = 62, Q_3 = 74; range: 37–84)
Sex (male)	28
Preexisting renal disease	24
ESRF/chronic dialysis treatment	4
Diabetes mellitus	12
Arterial hypertension	34
COPD	4
Hyperthyroidism	3
Hypothyroidism	3
Chronic atrial fibrillation	11
Preoperative hemoglobin <10 [g/dL]	16
Preoperative creatinine concentration [mg/dL]	1.49 (Q_1 = 1.05, Q_3 = 2.11; range: 0.62–6.18)
Type of surgery:	
Valvular surgery	23
Revascularization surgery (CABG and OPCABG)	7
Valvular + revascularization	6
Cardiac other	2
Vascular surgery including thoracic aorta surgery	10
Extracorporeal support (ECMO/VAD)	1
Heart transplant	1
Pericardial drainage	1
PM electrodes removal	1
Hospital mortality	29 (57%)

CABG — coronary artery bypass graft; COPD — chronic obstructive pulmonary disease; ECMO — extracorporeal membrane oxygenation; ESRF — end-stage renal failure; PM — pacemaker; OPCABG — off-pump coronary artery bypass graft; VAD — ventricular assist device

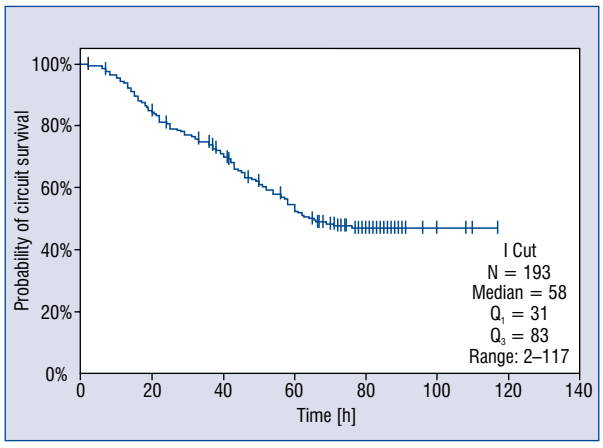

Figure 2. Kaplan-Meier curve of filter survival censored for discontinuation due to reasons other than circuit clotting.

agulation in postoperative cardiovascular surgery patients. It is safe and effective treatment leading to a median filter life of 58 h when adjusted for reasons other than clotting.

The present results compare well with similar studies, using RCA in a general intensive care unit (ICU) population (27 h) and postoperative cardiac surgical patients who received RCA predilution continuous hemofiltration (48 h), continuous hemodiafiltration with RCA or heparin (50–58 h) and continuous hemodialysis with RCA (39–61 h) [10, 14–20]. Most of these studies, however, did not specifically address the question of whether the patients received any systemic antithrombotic prophylaxis.

Although this is only a pilot study it is the first to demonstrate significant differences in RCA

Table 2. Systemic antithrombotic prophylaxis used during regional citrate anticoagulation continuous veno-venous hemofiltration sessions.

Antithrombotic agents	Number of hemofiltration sessions	Median circuit lifespan hours (range)
Group A (n = 56)		42 (2–91)
No antithrombotic medication	51	
ASA alone	5	
Group B (n = 62)		51 (7–117)
Prophylactic dose low molecular weight heparin (LMWH) without ASA	29	
Prophylactic dose LMWH with ASA	16	
Prophylactic dose fondaparinux without ASA	17	
Prophylactic dose fondaparinux with ASA	0	
Group C (n = 75)		
Treatment dose LMWH without ASA	44	79 (2–110)
Treatment dose LMWH with ASA	26	
Treatment dose fondaparinux without ASA	5	
Treatment dose fondaparinux with ASA	0	

ASA — acetylsalicylic acid; LMWH — low molecular weight heparin

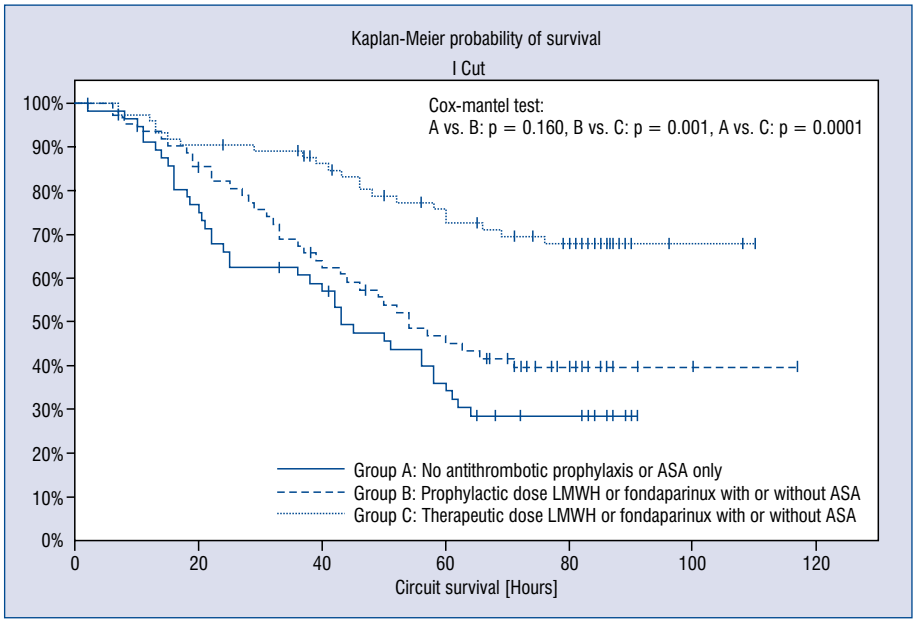

Figure 3. Influence of systemic antithrombotic prophylaxis on continuous renal replacement therapy (CRRT) circuit lifespan. (Group A: No antithrombotic prophylaxis or acetylsalicylic acid [ASA] only, Group B: prophylactic dose low molecular weight heparin [LMWH] or fondaparinux with or without ASA, Group C: more than prophylactic dose LMWH or fondaparinux with or without ASA).

CVVH filter lifespan between patients receiving additional systemic anticoagulation medications that are often required following cardiovascular surgery. This data is in line with a similar study of general ICU patients by Wu et al. [21] where the addition of low dose dalteparin to high volume predilution CVVH with RCA improved filter life span from 25 to 40 h, without increasing the risk of bleeding, and thus plays an important role when evaluating the success of specific filter anticoagulation or when comparing filter life span in cardiac patients and general ICU populations [21].

Table 3. Bleeding complications in the study group. Information on systemic antithrombotic prophylaxis refers to the highest dose during the whole hemofiltration treatment.

Type of bleeding	Surgical procedure	Systemic antithrombotic prophylaxis	Remarks	Survival
Hematoma of ascending colon mesentery	AVR, MVR	LMWH therapeutic dose		No
Airway bleeding (minor)	Cardiac sarcoma resection	LMWH therapeutic dose	Idiopathic thrombocytopenia before surgery	No
Airway bleeding (minor)	CABG	Fondaparinux prophylactic dose	HIT suspected	No
Retroperitoneal hematoma	MVR, TVP, ASD--closure, CABG	Fondaparinux therapeutic dose	Suspected relation to dialysis catheter inserted through femoral vein	No
Mediastinal hematoma, gastro-duodenal bleeding	AVR	No prophylaxis or ASA only		No
Airway bleeding (minor)	TVP	LMWH therapeutic dose		No
Airway bleeding and oral cavity mucosal bleeding (minor)	OPCABG	LMWH therapeutic dose, at 3rd session replaced with fondaparinux prophylactic dose	HIT suspected	No
Airway bleeding (minor)	MVR	LMWH therapeutic dose	Thrombocytopenia	No
Retroperitoneal bleeding in the iliopsoas muscle area	AVR	LMWH therapeutic dose	Suspected relation to dialysis catheter inserted through femoral vein	Yes
Oral cavity mucosal bleeding (minor)	AVR, CABG	LMWH therapeutic dose		No
Femoral hematoma after IABP removal	VA ECMO, IABP	UFH infusion	Myocarditis was an indication to VA ECMO	Yes
Retroperitoneal bleeding in the iliac muscle area 6 days after the end of hemofiltration treatment	MVR	LMWH therapeutic dose	HIT, endocarditis was an indication to MVR, bleeding 6 days after the end of hemofiltration. Suspected relation to dialysis catheter inserted through femoral vein	Yes

ASA — acetylsalicylic acid; ASD — atrial septal defect; AVR — aortic valve replacement; CABG — coronary artery bypass graft; HIT — heparin induced thrombocytopenia; IABP — intra aortic balloon pump; LMWH — low molecular weight heparin; MVR — mitral valve replacement; OPCABG — off-pump coronary artery bypass graft; TVP — tricuspid valve plastic; UFH — unfractionated heparin; VAD — ventricular assist device; VA ECMO — veno-arterial extracorporeal membrane oxygenation

The incidence of bleeding is an important marker of treatment safety during CRRT. RCA reduces bleeding complications but many postoperative cardiac patients receive additional anticoagulants [11]. In the current study, major and minor bleeding complications observed in 8 patients were related to treatment dose anticoagulation. High incidence of bleeding complications observed in the present group of patients treated with CRRT was unlikely to be related to CRRT circuit anticoagulation but to post cardiovascular surgery antithrombotic prophylaxis. It is a matter of ongoing discussion if LMWH or UFH bridging is indispensable after valve surgery [11].

An appropriately powered study to assess bleeding complications when prophylactic LMWH or fondaparinux is added, is needed before this can be recommended as a routine addition to RCA CRRT therapy to increase filter survival alone and this will be difficult to do. A limitation of the current study is that we assessed hemofiltration sessions during which different antithrombotic prophylaxis were compared. In some patients different antithrombotic regimens were used depending on their clinical status. For example, if the mechanical mitral valve replacement patient was treated with CRRT in the early postoperative hours due to anuria, no antithrombotic prophylaxis was used due to

the risk of bleeding. The same patient would however receive treatment dose of LMWH a few days later, often after the chest drains were removed. A more complex statistical comparison of bleeding episodes between the groups would be needed to evaluate the risk of bleeding post operatively, as well as a more formalized assessment of bleeding risk depending on time after surgery.

There are some clear limitations to this pilot study. It was not possible to capture data on catheter type and tip position, something which has been shown to play an important role in filter survival regardless of anticoagulation method [22].

Similarly, other factors potentially affecting circuit life span including platelet count and other measures of clotting function (e.g. analysis of thromboelastography) were not collected. Future studies of filter life span would benefit from including these laboratory data to determine if they are relevant in the clinical setting.

The life span of hemofiltration circuit can also be affected by multiple clinical factors including type of surgery, duration of surgery and cardiopulmonary bypass, aortic cross-clamp time, use of vasopressors, etc. A much larger study would be needed to individually evaluate these and it may not be of overall benefit.

There is however an additional potential benefit of demonstrating a good filter life span outcome with CVVH. A recent study revealed that after cardiac surgery postoperative inflammatory response is severe enough to fulfill systemic inflammatory response syndrome criteria in as many as 28% of patients [23]. Data from experimental and clinical studies, suggest that convection might be more effective than diffusion in the clearance of middle- and high-molecular weight particles at the equivalent dose, but the clinical benefit of convection above dialysis has not been shown [24].

In the original Royal London Hospital RCA protocol, a lower target citrate concentration (2.8 mmol/L) in the filter was accepted, in comparison to most RCA protocols for hemodialysis. ACD-A citrate solution was used instead of trisodium citrate solution, most commonly used throughout Europe, in order to reduce the risk of metabolic alkalosis resulting from citrate metabolism, and to decrease sodium load. It was presumed that target citrate concentration in the filter equal to 2.8 mmol/L should decrease ionized calcium concentration in the filter to 0.35 mmol/L on the average.

Some modifications were made to the original Royal London CVVH with RCA treatment formula. Firstly, actual body weight instead of ideal body weight was used for renal dose calculation. The rationale for it was that patients after recent cardiovascular surgery have significant catabolism, and the authors intended to use a higher clearance, rather than too low of a clearance of solutes.

Secondly, the target plasma calcium concentration was higher in comparison to the original protocol. In order to achieve this goal, calcium concentration in calcium replacement solution was stepwise increased after initial experience, from 4.6 mmol/L to a final 18.4 mmol/L. Higher range of target calcium concentration could potentially slightly increase the risk of filter clotting, because with a higher plasma ionized calcium concentration and equal dose of citrate, ionized calcium concentration in the filter could also be slightly increased in comparison to the observations of the authors of the original protocol. A target plasma ionized calcium concentration was increased in order to minimize the risk of hypocalcemia, which could contribute to exacerbating post cardiotomy heart failure and cause calcium resorption from bones during prolonged treatment of patients immobilized by their critical condition.

Hight cut-off (55 kDa) filters used in the study patients might theoretically promote convective cytokine removal, but its efficacy was not specifically studied in post cardiac surgery patients with AKI. This effect may be beneficial in the early postoperative hours after cardiopulmonary bypass cardiac surgery where high concentrations of cytokines and chemokines can play a significant role in contributing to increased postoperative morbidity and mortality and using the present protocol may be a way, in future, of evaluating its potential benefit [25, 26]. To add further impetus in performing this type of study, there is some experimental rationale to preference RCA when initiating CRRT for postoperative cardiac patients. RCA is related to less complement and neutrophil activation in comparison to heparin, which may be an important factor in cardiac surgery patients, in whom complement and neutrophil activation by cardiopulmonary bypass, contributes to postoperative complications [27]. Citrate has been shown to exert cardio- and reno-protective effects in AKI triggered by ischemia-reperfusion in rats but this is yet to be shown in the clinical setting [28]. An improvement of survival in critically ill surgical patients treated with RCA in comparison to LMWH was observed by Oudemans-Van Straaten but it was not confirmed by subsequent studies [4, 29].

Conclusions

In summary, postdilution CVVH RCA for postoperative cardiovascular surgery patients results in excellent filter life span when compared to data from other groups of similar patients. The addition of treatment dose LMWH/fondaparinux required for post cardiac surgery antithrombotic prophylaxis significantly increases filter life span, but may carry a risk of increased incidence of bleeding episodes. Further studies are needed to determine whether routine additional anticoagulation is beneficial and whether a CVVH postdilution RCA protocol, that affords long filter life spans, can add additional mortality and morbidity benefit to postoperative cardiac surgical patients with renal failure over other modes of CRRT.

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Effectiveness and safety of PCSK9 inhibitor therapy in patients with familial hypercholesterolemia within a therapeutic program in Poland: Preliminary multicenter data

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Abstract

Background: *In Poland, treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has become available free of charge in a therapeutic program. Assessed herein, is the efficacy and safety of alirocumab and evolocumab in patients with heterozygous familial hypercholesterolemia (FH).*

Methods: *Data of 55 adult FH patients who participated in the program were analyzed upon meeting the criteria established by the Ministry of Health (low density lipoprotein cholesterol [LDL-C] above 160 mg/dL on max. tolerated statin dose and ezetimib). The efficacy of PCSK9 inhibitors in reducing LDL-C with drug administration every 2 weeks was assessed after 3 months and 1 year of therapy. A safety profile evaluation was performed at each visit. 48 patients completed the 3-month and 21 for the 1-year observation periods (34 patients treated with alirokumab and 14 with evolocumab).*

Results: *The mean concentration of direct-measured LDL-C decreased from the initial level of 215.1 ± ± 74.5 mg/dL to 75.3 ± 64.1 mg/dL, i.e., by 65 ± 14% following 3 months of treatment. This effect was stable in 1-year observation (77.7 ± 72.8 mg/dL). Adverse effects were flu-like symptoms (13.0%), injection site reactions (11.1%), fatigue (5.6%) and musculoskeletal symptoms (5.6%). Seven patients failed to complete the 3-month treatment period due to side effects or non-compliance, and 1 patient failed to complete the 1-year treatment due to myalgia.*

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Conclusions: *This study confirmed high effectiveness of PCSK9 inhibitors in reducing LDL-C levels in patients with FH. Due to restrictive inclusion criteria with LDL-C threshold level > 160 mg/dL (> 4.1 mmol/L) required for participation in the therapeutic program, a relatively small number of FH patients were eligible for treatment.* (Cardiol J 2022; 29, 1: 62–71)

Key words: familial hypercholesterolemia, PCSK9 inhibitors, alirocumab, evolocumab, LDL-cholesterol reduction, clinical side effects

Introduction

Cardiovascular (CV) diseases (CVD) account for 46% of all deaths in Poland [1]. The low-density lipoprotein cholesterol (LDL-C) level is one of most important CVD risk factors and lowering this level remains a key point in CV risk reduction [2]. The intensity of hypolipemic therapy and LDL-C treatment goals varies depending on the CV risk category [3]. For people at very-high and high (CV) risk LDL-C should be decreased < 55 mg/dL (< 1.4 mmol/L) and < 70 mg/dL (< 1.8 mmol/L), respectively and reduced ≥ 50% from baseline. Individuals with familial hypercholesterolemia (FH) and atherosclerotic CVD or other major risk factors, are at very-high CV risk, but those without other major risk factors are at high risk. FH is a quite common genetic disorder with a prevalence of approximately 1 in 250 adults in Poland [4]. It is estimated that the disease affects over 136,000 adults [5]. The prevalence of FH in the Polish population is very similar to the recent worldwide data (1 in 311–313 individuals) [6, 7]. However, FH remains underdiagnosed and undertreated, and many patients fail to achieve the target LDL-C level despite intensive statin therapy even in combination with ezetimibe [5, 8]. In such situations the new therapeutic strategy may be the addition of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors [2]. It has been shown that PCSK9 inhibitors (evolocumab and alirocumab) reduce LDL-C level on average by 60% [9, 10]. According to 2019 European Society of Cardiology/European Society of Atherosclerosis (2019 ESC/EAS) guidelines for the management of dyslipidemias PCSK9 inhibitors are recommended in very-high risk patients with FH if the treatment goal is not achieved on maximal tolerated statin with ezetimibe. PCSK9 inhibitors are also recommended in FH patients who do not tolerate statins [3]. In contrary to recent ESC/EAS guidelines, a Polish group of experts, in a statement from 2016, recommended PCSK9 inhibitors implementation in patients with heterozygous FH (HeFH) if LDL-C levels are above 160 mg/dL (4.1 mmol/L) on high-intensity statin treatment (atorvastatin 40–80 mg/d or rosuvastatin 20––40 mg/d) [11]. This statement was considered by the Polish Ministry of Health when defining criteria of a new PCSK9 therapeutic program for patients with FH that is currently financed by the National Health Found.

The aim of the current observational study was to assess PCSK9 inhibitors efficacy and safety among Polish FH patients participating in a drug/ /therapeutic program for patients with FH.

Methods

Fifty-five adult patients with FH and LDL-C levels > 160 mg/dL (> 4.1 mmol/L) were qualified for the drug program with alirocumab or evolocumab (from March 2019 to January 2021) under the National Center for Familial Hypercholesterolemia (Gdansk), The National Institute of Cardiology (Warsaw) and University Hospital (Krakow). 43 patients were receiving high-intensity statin treatment for at least 6 months, and 10 patients were on the maximum tolerated dose of a statin, 2 patients did not use statin due to total intolerance. Rosuvastatin was taken in dose 40 mg per day by 32 patients, 20 mg by 3 patients, lower doses — 5 patients (15 mg — 1 patient, 5 mg — 2 patients, < 5 mg per day — 2 patients). Atorvastatin was taken in doses of 80 mg per day by 3 patients, 60 mg by 1 patient, 40 mg by 4 patients, 20 mg by 1 patient, 10 mg by 2 patients, lower doses than 10 mg/day by 2 patients. Three patients did not use ezetymibe. Two of them were patients with statin intolerance (one did not use statin, one used atorvastatin in a dose of < 10 mg per day). One patient was on high-intensity statin — rosuvastatin 20 mg. Intolerance to standard therapy has always been reliably confirmed by the patient's physician (general practitioner or cardiologist). The described baseline hypolipemic therapy was not altered during the trial. All patients received alirocumab or evolocumab subcutaneously every 2 weeks at a dose of 150 mg or 140 mg, respectively. The evaluation of the treatment effectiveness was assessed after 2 and 4 weeks and obligatorily after

Table 1. Characteristics of patients prior to study entry (n = 55).

Characteristic	Mean (SD) or n (%)	Median (IQR)
Age (years)	54.8 (11.1)	54.0 (47.5–61)
Female (n, %)	26 (47.3)	
BMI [kg/m^2]	28.5 (4.4)	28.0 (25.0–31.8)
Waist (n = 32)	97.9 (12.4)	95.5 (89.0–104.8)
SBP [mmHg]	134.5 (14.4)	134.0 (127.0–142.4)
DBP [mmHg]	82.7 (9.6)	82.0 (75.0–88.0)
HR/min (n = 51)	70.7 (9.0)	70.0 (65.0–75.5)
TC [mg/dL]	314.0 (83.3)	294.0 (244.5–357.5)
LDL-C [mg/dL] (direct) (n = 50)	237.4 (80.1)	209.0 (180.5–267.8)
LDL-C [mg/dL] (calculated)	224.1 (79.1)	192.0 (173.2–255.0)
HDL [mg/dL]	47.9 (14.7)	48.0 (38.0–55.5)
TG [mg/dL]	211.2 (154.5)	154.0 (130.0–231.0)
apo B [g/dL] (n = 32)	1.7 (0.5)	1.6 (1.3–1.9)
Lp(a) [g/dL] (n = 44)	0.7 (0.7)	0.3 (0.2–1.0)
Glucose [mg/dL] (n = 48)	100.3 (21.6)	94.5 (86.0–108.5)
Creatinine [mg/dL]	0.9 (0.2)	0.8 (0.8–1.0)
GFR [mL/min] (n = 48)	80.7 (13.3)	90.0 (75.3–90.0)
ALT [U/L] (n = 54)	34.4 (23.1)	28.5 (21.0–42.0)
AST [U/L] (n = 45)	26.3 (10.1)	25.0 (19.0–31.0)
CK [U/L] (n = 54)	153.0 (113.7)	126.0 (69.3–192.8)
CRP [g/L] (n = 32)	2.6 (2.6)	1.5 (0.7–3.7)
TSH [μU/mL] (n = 49)	1.2 (0.9)	1.1 (0.7–1.6)

ALT — alanine aminotransferase; apo B — apolipoprotein B; AST — aspargine aminotransferase; BMI — body mass index; CK — creatine kinase; CRP — C-reactive protein; DBP — diastolic blood pressure; GFR — glomerular filtration rate; HbA1c — glycated hemoglobin; HDL-C — high density lipoprotein cholesterol; HR — heart rate; IQR — interquartile range; LDL-C — low density lipoprotein cholesterol; Lp(a) — lipoprotein (a); SBP — systolic blood pressure; SD — standard deviation; TC — total cholesterol; TG — triglycerides; TSH — thyreotropic hormone

3 months and 1 year of therapy. The safety of the therapy was assessed at each visit.

LDL-C concentrations were calculated both from Friedewald's formula and was determined using the direct method. Hospital medical records were used for demographic and clinical characteristics of patients.

This retrospective study was based on analysis of medical records of all consecutive patients enrolled to therapeutic program. All subjects included into the program were informed about the purpose of the program and signed informed consent. The conducted data analysis and therapeutic program were approved by Ministry of Health and strictly followed binding requirements.

Statistical analysis

Continuous data were presented as a mean value and standard deviation (SD), as well as a median and interquartile range (IQR). Categorical data were presented as a number and percentages. Continuous paired data were compared by the Wilcoxon test and independent data were compared by the Mann-Whitney U test. P value of less than 0.05 was considered statistically significant. Data was analyzed using the R software v. 3.6.3.

Results

Demographic and baseline characteristics of patients are summarized in Table 1. FH was diagnosed in patients with > 8 points according to Dutch Lipid Clinic Network (DLCN) criteria; Median DLCN score was 12.0 (10.0–15.0) points without genetic testing and 18 (14.0–19.0) points with performed genetic results. Figure 1 presents the prevalence of individual criteria for the diagnosis of FH in the study participants. 36 out of 55 patients were diagnosed with genetic variant responsible for FH: 91.6% in the LDL (n = 33) receptor (LDLR) gene and 2.4% (n = 3) in the apolipoprotein B (APOB) gene. In the remaining

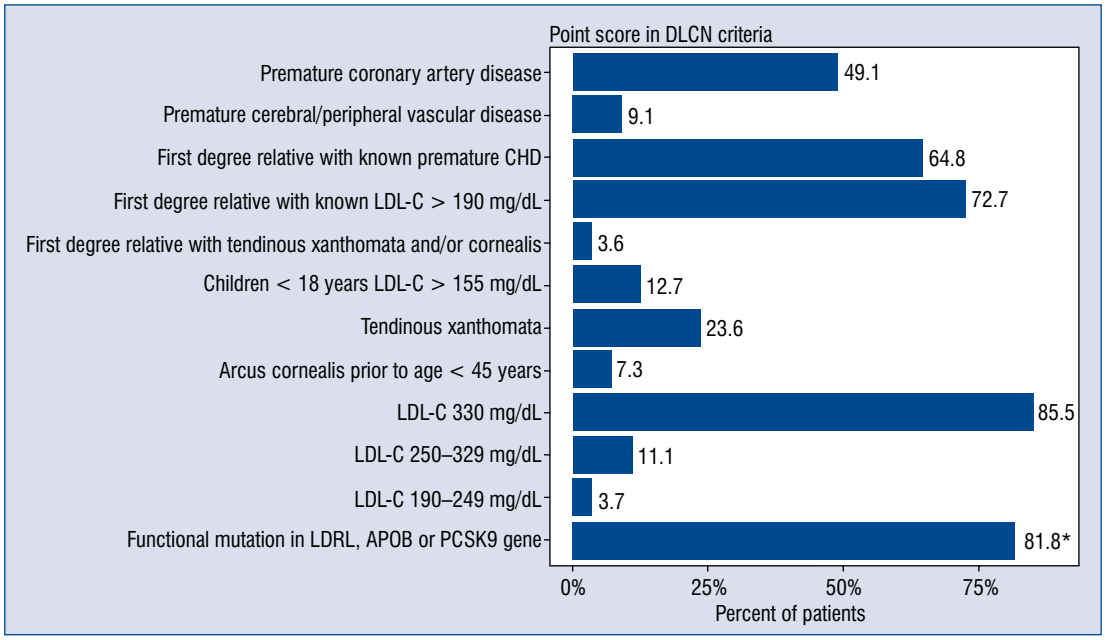

Figure 1. The prevalence of Dutch Lipid Clinic Network (DLCN) familial hypercholesterolemia criteria (point score) in patients under study; *Among patients referred to genetic testing; abbreviations — see text.

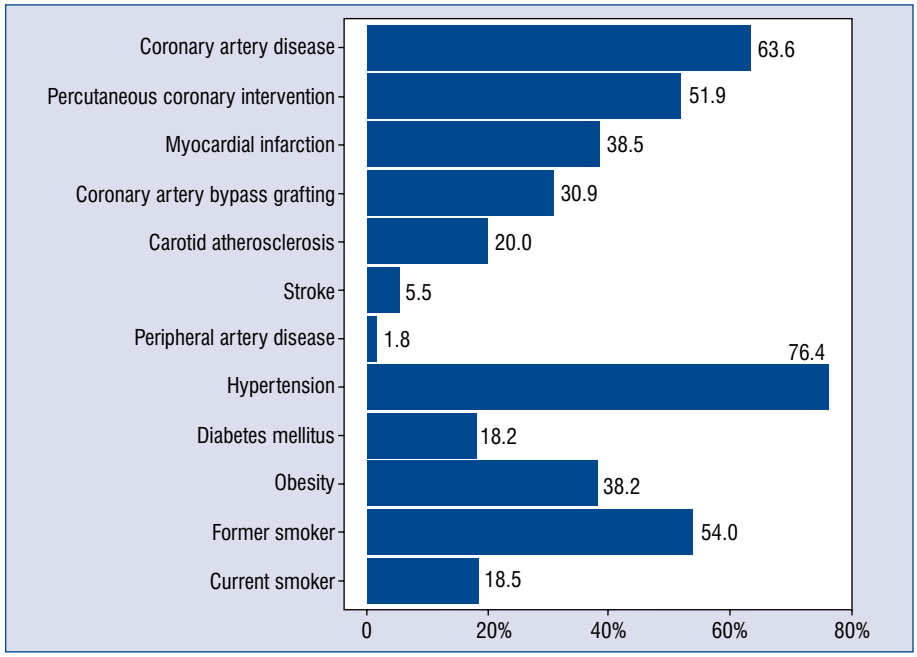

Figure 2. The prevalence of selected cardiovascular diseases, end-points and risk factors in familial hypercholesterolemia patients.

cases the causing mutation was not found (n = 8) or genetic test was not performed (n = 11). 71.4% of patients had a family history of hypercholesterolemia. 63.6% of patients had already established coronary artery disease (CAD), 49.1% had premature CAD, 20% were diagnosed with carotid atherosclerosis and 5.5% with stroke (Fig. 2). Among the assessed risk factors, arterial hypertension was the most common (76.4%). 38.2% of patients were diagnosed with obesity and 18.2%

Table 2. Effects of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors on low density lipoprotein-cholesterol (LDL-C) level after 3 months therapy as added to statin and ezetymibe in familial hypercholesterolemia patients and baseline LDL-C > 160 mg/dL (> 4.1 mmol/L) (n = 48).

Lipid	Mean (SD)		P	Reduction (%)/ /Increase (%)
	Before	After (3 months)		
LDL-C [mg/dL] (calculated)	215.1 (74.5)	75.3 (64.1)	< 0.001	65.0 (14.0)
LDL-C [mg/dL] (direct measurement)	228.2 (76.2)	82.1 (62.5)	< 0.001	64.0 (18.0)
Triglycerides [mg/dL]	222.2 (161.7)	160.0 (110.8)	< 0.001	28.0 (31.5)
HDL-C [mg/dL]	47.2 (15.1)	51.8 (16.0)	0.003	9.7 (6.0)
Non-HDL-C [mg/dL]	259.3 (80.8)	106.3 (69.3)	< 0.001	59.0 (14.2)

HDL-C — high density lipoprotein-cholesterol; SD — standard deviation

had diabetes. The mean LDL-C (Friedewald formula) before administration of PCSK9 inhibitors was 224.1 (79.1) mg/dL and the median was 192.0 (173.2–255.0) mg/dL, and adequate for the direct method 237.4 (80.1) mg/dL and 209.0 (180.5–267.8) mg/dL, respectively. The mean concentration of triglycerides was 211.2 (154.5) mg/dL, and the median was 154.0 (130.0–231.0) mg/dL while high density lipoprotein cholesterol (HDL-C) was 47.9 (14.7) mg/dL and 48.0 (38.0–55.5), respectively. In addition to lipid-lowering therapy, 38 patients were on angiotensin converting enzyme inhibitors or angiotensin-II-receptor antagonists, 36 on beta-blockers and 34 on acetylsalicylic acid; 11 patients were treated with a P2Y12 inhibitor.

The effectiveness of treatment was assessed after 3 months in 48 patients, 7 patients could not be tested after this obligatory period as they did not complete the study. Mean lipid levels before and after treatment and the mean reduction are presented in Table 2, while Figure 3 presents the effects of PCSK9 inhibitors on LDL-C levels in individual patients. Figure 4 presents the concentration of LDL-C after 2 and 4 weeks and after 3 months of therapy. As shown in Table 2, after 3 months of treatment with PCSK9 inhibitors, the mean calculated LDL-C concentration decreased significantly from 215.1 ± 74.5 mg/dL to 75.3 ± ± 64.1 mg/dL, i.e., by 65.0 ± 14.0% ($p < 0.001$), and when measured directly decreased from the 228.2 ± 76.2 mg/dL to 82.1 ± 62.5 mg/dL, i.e., by 64.0 ± 18.0% ($p < 0.001$). The median calculated LDL-C decreased from 187.0 mg/dL (171.5–241.3) to 64.8 mg/dL (37.7–86.2), i.e., by 70.9% (54.1––79.9), and measured directly from 204.5 mg/dL (178.8–262.5) to 71.5 mg/dL (43.5–93.5), i.e., by 68.2% (53.8–79.4). Therapeutic target was deemed achieved when at least one LDL-C result (calculated or directly determined) was < 55 mg/dL (<1.4 mmol/L) or < 70 mg/dL (< 1.8 mmol/L) for very-high and high CV risk patients, respectively. 25 (52%) patients out of 48 achieved the therapeutic target, including 16 patients reaching levels below 55 mg/dL and 9 patients below 70 mg/dL (Fig. 3). The individual response to treatment with PCSK9 inhibitors was varied and ranged from 30.2% to 90% of LDL-C decrease. As presented in Figure 4, the greatest therapeutic effect was achieved after 2 weeks (following the first dose of drug), and the difference in the result after 4 weeks and 3 months, was insignificant in relation to the effect after 2 weeks. In Figure 5 we see the threshold values for LDL-C concentration (> 160 mg/dL) making patients with FH eligible for the drug program with alirocumab and evolocumab compared with the thresholds recommended by 2017 ESC Task Group Guidelines [12]. Figure 5 also presents LDL-C levels before and after 3 months of treatment with PCSK9 inhibitors. The largest reduction in LDL-C occurred after the first drug administration, amounting to an average of 56.6%. Patients on the maximum tolerated dose of statins (n = 11) had significantly higher initial mean LDL-C levels than patients on intensive statin therapy (n = 37), i.e. calculated LDL-C of 253.7 ± 91.7 mg/dL and that directly measured of 264.7 ± 95.7 mg/dL vs. 203.7 ± ± 65.7 mg/dL and 217.4 ± 67.1 mg/dL ($p = 0.008$ and $p = 0.04$, respectively). Following 3 months of PCSK9 inhibitors therapy, the concentration of LDL-C in the group treated with the maximum tolerated dose of statin was significantly higher than in the high intensity therapy group, with calculated levels of 110.3 ± 75.6 mg/dL vs. 64.9 ± 57.3 mg/dL and when measured directly 118.6 ± 74.6 mg/dL vs. 71.2 ± 55.0 mg/dL (both $p = 0.002$). Table 3 presents adverse effects that occurred during treatment. These included mainly flu-like symptoms (n = 7, 13%) and injection site reactions (n = 6, 11%).

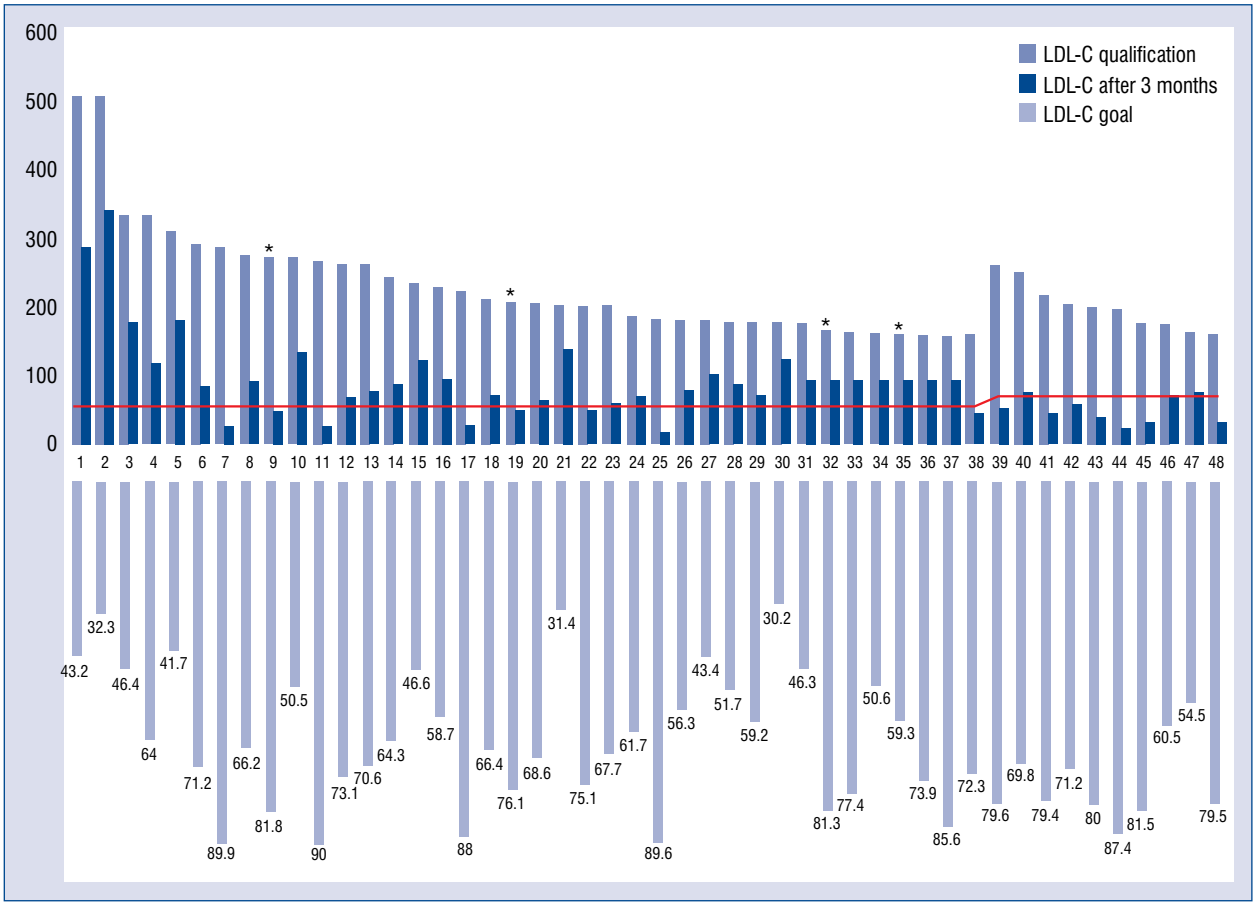

Figure 3. Effect of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors on low density lipoprotein-cholesterol (LDL-C) concentration and percent reduction in individuals after 3 months of therapy. The red line denotes the treatment goals for LDL-C concentrations of < 55 mg/dL (< 1.4 mmol/L) and < 70 mg/dL (< 1.8 mmol/L); black asterisk — no data of direct LDL-C (taken calculated LDL-C).

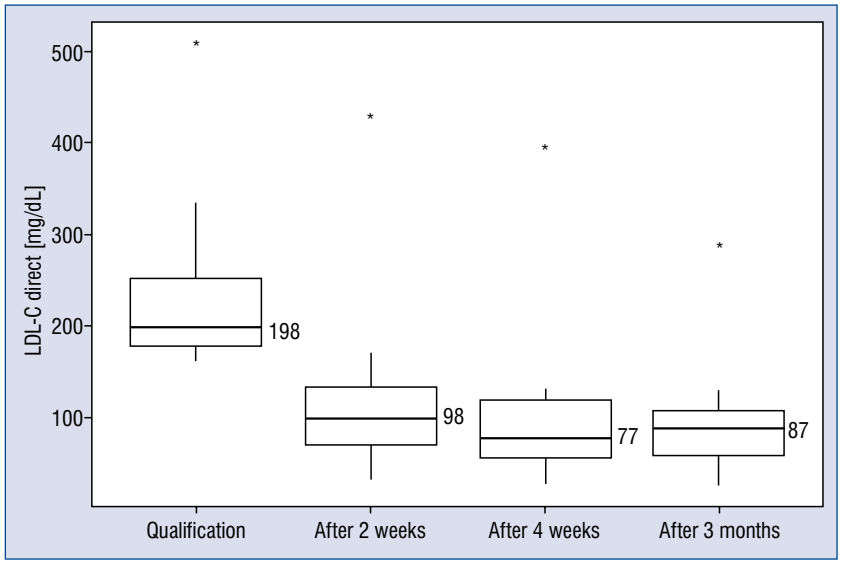

Figure 4. Low density lipoprotein-cholesterol (LDL-C) before and after 2 and 4 weeks and 3 months of treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors.

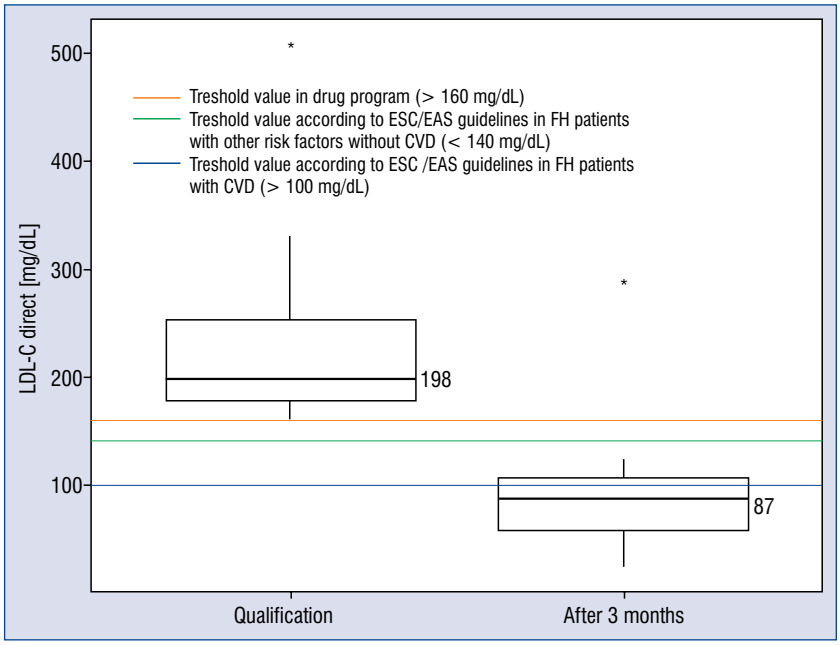

Figure 5. Low density lipoprotein-cholesterol (LDL-C) before and after 3 months of treatment with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors and threshold values propose for starting PCSK9 inhibitor therapy; CVD — cardiovascular disease; ESC/EAS — European Society of Cardiology/European Society of Atherosclerosis; FH — familial hypercholesterolemia.

Table 3. Number of patients who reported, at least once, the respective adverse effect (100% represents 55 patients included in the treatment).

Side reaction	N (%)
Flu-like symptom	7 (13.0%)
Injections site reactions	6 (11.1%)
Fatigue	3 (5.6%)
Musculoskeletal symptoms	3 (5.6%)
Nasopharyngitis	1 (1.9%)
Gastrointestinal symptoms	1 (1.9%)
Erectile dysfunction	1 (1.9%)
Hot flashes	1 (1.9%)
Allergic reaction	3 (5.5%)
Discontinuation because of side effects	4 (7.4%)
Others	2 (3.6%)
All discontinuation	8 (14.5%)

Side effects were the cause of drug discontinuation in 3 patients in 3-month follow-up and in 1 patient in a 1-year follow-up (2 allergic reactions, problems with blood pressure fluctuation and myalgia). Two patients did not achieve a 30% reduction of LDL-C and 2 patients discontinued the drugs because of non-compliance. No CV events were observed during the observation period.

Discussion

Here, for the first time, real-world data on the effectiveness and safety of PCSK9 inhibitor therapy is presented in patients with FH from Poland.

The addition of PCSK9 inhibitors to lipid-lowering therapy (statin ± ezetimibe) represents progress in therapeutic efforts to reach the recommended LDL-C levels. This is particularly important in patients with FH, who are at a higher risk of premature CVD due to their high cholesterol exposure lasting from birth [13]. Despite being treated with the maximum or maximum tolerated dose of statin plus ezetimibe, FH patients still presented LDL-C concentrations far from the target value. The requirements for the inclusion criteria for the PCSK9 inhibitors drug program regarding the concentration of LDL-C are very strict, i.e. LDL-C > 160 mg/dL. Even among patients treated at National Center for Familial Hypercholesterolemia with the molecular test as the standard diagnostic method and highest number of genetically confirmed patients, only 7.6% of probands with definite diagnosis and 4.7% of all patients with FH (probands and family members) met the conditions for participation in the program. This baseline LDL-C criterion influenced the study results, as only 25 from 48 of patients

(52%) achieved the LDL-C goal, 16 patients < 55 mg/dL (< 1.4 mmol/L) and 9 patients < 70 mg/dL (< 1.8 mmol/L). According to the European guidelines for the management of dyslipidemia [3], it is recommended for patients with FH in secondary prevention to achieve LDL-C of < 55 mg/dL (< 1.4 mmol/l) (IC). The same therapeutic target should also be considered in FH patients in primary prevention in the presence of another additional major risk factor [3]. Other patients with FH are high CV risk patients with the recommended LDL-C target value of < 70 mg/dL (< 1.8 mmol/L). European experts recommend adding a PCSK9 inhibitor to therapy with the maximum tolerated dose of statin and ezetimibe in FH patients with a very high risk whenever the LDL-C levels are above the target value [3].

Treatment of FH patients with alirocumab and evolocumab was assessed in the placebo-controlled ODYSSEY FH I and II [14], in the ODYSSEY HIGH FH [15] and in the RUTHEFORD [16] clinical trials. Compared to the present cohort, a clear difference between the studies appeared in the diagnosis of FH. In the ODYSSEY trials, a different percentage of patients had genetic confirmation of the FH diagnosis, i.e., 39.9% (FH I), 70.1% (FH II) and 17.8% (HIGH FH), compared to 60% in the current work. There were also differences in the incidence of coronary heart disease. In the clinical trials the percentages were 45.5%, 34.7%, and 43.1% in the alirocumab arm, respectively, while in the drug program it was 63.6%. In ODYSSEY FH I and FH II, the mean baseline LDL-C concentration at the maximum tolerated dose of statin ± other lipid-lowering drug was 144.7 mg/dL and 134.6 mg/dL, respectively, so it was lower than in the drug program and it decreased after 24 weeks of treatment in FH I to 71.3 mg/dL (on average by 57.9%, placebo corrected), in FH II to 67.7 mg/dL (on average by 51.4%, placebo corrected) [14], while after 12 weeks in the drug program to 82.1 mg/dL (direct measurement), i.e., by an average of 65.0% and up to 75.3 mg/dL (LDL-C calculated), i.e., by an average of 64.0% (Table 2). LDL-C levels of < 70 mg/dL (< 1.8 mmol/L) were achieved by 59.8% of patients in FH I and 68.2% of patients in FH II, however the baseline LDL-C was lower and the therapeutic targets were milder to be achieved. Patients with LDL-C concentrations of over 160 mg/dL, similar to the present research, were included in the ODYSSEY HIGH FH [15]. The patients in the current study had to additionally be on ezetimibe for at least 1 month, but in ODYSSEY HIGH FH there was no such requirement. Mean LDL-C levels in those treated with alirocumab for over 24 weeks decreased from 196.3 mg/dL to 107 mg/dL, i.e. by 45.7%, and 32% of patients reached LDL-C levels lower than 70 mg/dL. In the present study, the reduction in LDL-C was greater and the lower values were achieved after 12 weeks of treatment. It is also true if the present results are compared with the RUTHERFORD trial, where patients receiving evolocumab plus standard of care experienced a mean 53.6% reduction LDL-C after 48 weeks [16].

Data on the use of PCSK9 inhibitors in clinical practice is limited, and the groups investigated so far were small — from 38 to 271 patients. The eligibility criteria for reimbursed treatment differ depending on the country, local epidemiological conditions and the budgetary capacity of the system. Depending on the CV risk and comorbidities, patients with LDL-C levels of 70–190 mg/dL were qualified for treatment [17–23]. Among the available publications, only one cohort described only patients with FH [21], in the remaining cases the percentage of these patients amounted to 51.5––89.0%. The studied populations were very similar in terms of their age — the average was 55–62 years, similar to the cohort in the present study. The incidence of CV diseases was 37.0–75.2%. 94.7% in the German study, which included patients with atherosclerotic plaques in the carotid arteries and in the aorta [16], whereas the incidence of CAD in the Polish program was 63.6%. Compared to other publications, hypertension was more common in the Polish population — 76.4% vs. 30.5–63.0%, and the incidence of diabetes was higher in only 1 case — in the Israeli study [23] — 31%, in Poland this percentage amounted to 18.2%. It is worth mentioning the recently published open-label ODYSSEY APPRISE trial with only one arm, i.e. patients treated with alirocumab without placebo [24]. This real-world setting study included 636 patients with HeFH and 358 patients without FH, who were treated with alirocumab at doses of 75–150 mg every 2 weeks. Statins were taken by 87% of patients with FH and 56.7% of those without FH. The proportions of patients taking ezetimibe were 69.3% and 41.3%, respectively. In patients with FH, the mean baseline LDL-C decreased from 196.3 mg/dL by 53.4% after 12 weeks of treatment with alirocumab, and in patients without FH from 157.3 mg/dL by 57.6%. LDL-C was reduced below 1.8 mmol/L in 69.1% of patients overall, and for 64.7% and 77.4% of the HeFH and non-FH subgroups, respectively.

All patients who continued the current program experienced a significant decrease in LDL-C,

Table 4. Effects of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors on low density lipoprotein-cholesterol (LDL-C) level (3 months vs. 1 year) therapy as added to statin and ezetymibe in familial hypercholesterolemia patients and baseline LDL-C > 160 mg/dL (> 4.1 mmol/L) (n = 21).

Lipid	Mean (SD)		P
	After 3 months	After 1 year	
LDL-C [mg/dL] (calculated)	72.1 (74.4)	71.8 (73.9)	0.602
LDL-C [mg/dL] (direct measurement)	78.9 (71.2)	77.7 (72.8)	0.970
Triglycerides [mg/dL]	146.3 (98.4)	122.4 (44.8)	0.211
HDL-C [mg/dL]	45.9 (10.1)	45.2 (9.5)	0.904

HDL-C — high density lipoprotein-cholesterol; SD — standard deviation

and 52% of patients even achieved the LDL-C goal. The greatest therapeutic effect was achieved 2 weeks following the inclusion of PCSK9 inhibitors, with a reduction of direct LDL-C by an average of 57.8 (18.6)% (median 56.9% [45.6–70.5%]). After 3 months and 1 year a slight additional effect was also secured, achieving a decrease by an average of 65.5 (16.3)% (median 68.2% [53.8–79.4%]) and 66.9 (18.7)% (median 75.5% [55.6–81.3%]) respectively compared to baseline (Table 4). Median LDL-C values in subsequent determinations are presented in Figure 4. The rate of decrease in LDL-C levels seems to be consistent with clinical trials with evolocumab (FOURIER) and alirocumab (ODYSSEY OUTCOMES; ODYSSEY LONG TERM) [9, 10, 25]. In the FOURIER study, LDL-C decreased from the median baseline value of 92 mg/dL by an average of 57% after 4 weeks, and by 61% after 12 weeks [9]. In the ODYSSEY LONG TERM study, the difference between the alirocumab and placebo groups in the mean percentage change from baseline in calculated LDL-C level was 62% after 24 weeks [24]. The LDL-C levels qualifying patients for FOURIER, ODYSSEY OUTCOMES and ODYSSEY LONG TERM clinical trials were different than in the present study [9, 10, 25]. Very high-risk patients received treatment with PCSK9 inhibitors if the therapeutic target was not achieved, which, according to the then recommendations, was LDL-C < 70 mg/dL in secondary prevention. In the ODYSSEY FH I and FH II studies [14], the target LDL-C levels were < 70 mg/dL or < 100 mg/dL, depending on the clinical profile of the volunteer (CVD present or absent).

The long-term safety and efficacy for evolocumab in patients with FH were confirmed in another study where 194 severe HeFH and 106 with homozygous FH (HoFH), that included 14 < 18 years of age patients were enrolled [26]. In this open-label, single-arm study, patients on stable lipid-lowering therapy were given subcutaneous evolocumab 420 mg monthly or 420 mg every 2 weeks if on lipoprotein apheresis. Mean change in LDL-C from baseline to week 12 was –54.9% (–104.4 mg/dL) in those with severe HeFH and –21.2% (–59.8 mg/dL) in patients with HoFH. Evolocumab was well tolerated over a median of 4.1 years.

Despite of careful implementation of the study design and further thorough analysis of the data the study remains observational. Another limitation was constituted by the small group of patients. This was the result of restrictive inclusion criteria for the therapeutic program.

The first Polish clinical observation demonstrates that the strong lipid-lowering effect of both PCSK9 inhibitors was confirmed in patients, while the LDL-C concentration threshold for inclusion in the therapy should correspond to the European recommendations.

Conclusions

Polish patients achieved a significant reduction in LDL-C concentrations (68%) following treatment with PCSK9 inhibitors, which was stable over time. The treatment targets set out in the dyslipidaemia management guidelines were met with the addition of PCSK9 inhibitors in 52% of patients with high baseline LDL-C on statin therapy (maximum or maximum tolerated) in combination with ezetimibe. Due to inclusion criteria, which are very restrictive and inadequate to the real clinical needs, the percentage of FH patients, who could benefit from treatment with PCSK9 inhibitors, is very limited. Assuming that there are approximately 150,000 people with FH in Poland, only 0.1% of this population could benefit from reimbursed treatment with PCSK9 inhibitors. At the National Center for Familial Hypercholesterolemia, there were 24 eligible patients (7.6% of the probands and 4.7% of all FH

patients-unpublished data of National Center for Familial Hypercholesterolemia in Gdansk).

Conflict of interest: None declared

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A patient-centered multidisciplinary cardiac rehabilitation program improves glycemic control and functional outcome in coronary artery disease after percutaneous and surgical revascularization

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Abstract

Background: *Cardiac rehabilitation (CR) is strongly associated with all-cause mortality reduction in patients with coronary artery disease (CAD). The impact of CR on pathological risk factors, such as impaired glucose tolerance (IGT) and functional recovery remains under debate. The aim of the present study is to determine whether CR had a positive effect beside physical exercise improvement on pathological risk factors in IGT and diabetic patients with CAD.*

Methods: *One hundred and seventy-one consecutive patients participating in a 3-month CR from January 2014 to June 2015 were enrolled. The primary endpoint was defined as an improvement of peak workload and VO2-peak; glycated hemoglobin (HbA1c) reduction was considered as secondary endpoint.*

Results: *Euglycemic patients presented a significant improvement in peak workload compared to diabetic patients (from 5.75 ± 1.45 to 6.65 ± 1.84 METs vs. 4.8 ± 0.8 to 4.9 ± 1.4 METs , $p = 0.018$). VO2-peak improved in euglycemic patients (VO2-peak from 19.3 ± 5.3 to 22.5 ± 5.9 mL/min/kg, $p = 0.003$), while diabetic patients presented only a statistically significant trend (VO2-peak from 16.9 ± 4.4 to 18.0 ± 3.8 mL/min/kg, $p < 0.056$). Diabetic patients have benefited more in terms of blood glucose control compared to IGT patients (HbA1c from 7.7 ± 1.0 to 7.4 ± 1.1 compared to 5.6 ± 0.4 to 5.9 ± 0.5, $p = 0.02$, respectively).*

Conclusions: *A multidisciplinary CR program improves physical functional capacity in CAD setting, particularly in euglycemic patients. IGT patients as well as diabetic patients may benefit from a CR program, but long-term outcome needs to be clarified in larger studies.* (Cardiol J 2022; 29, 1: 72–79)

Key words: cardiac rehabilitation, coronary artery disease, diabetes mellitus, reduced glucose tolerance, cardiopulmonary test

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Introduction

Cardiovascular disease and acute coronary syndrome (ACS) represent a major source of morbidity and mortality in Western countries [1]. Cardiac rehabilitation (CR) has been strongly associated with a reduction in all-cause mortality in patients with coronary artery disease (CAD), hospital readmissions, costs and improvement in exercise capacity, quality of life and psychological well-being [2–5]. Therefore, CR is currently a mainstay of post-acute care strategy and is recommended by international guidelines for stable CAD (Class I, Level A). A multi-factorial intervention including patient assessment, physical activity/ /diet/nutritional counselling, exercise training, risk factor control, patient education, psychosocial management, and vocational advice are also recommended for patients with ST-elevation acute myocardial infarction (Class I, Level B), and non ST-elevation myocardial infarction (Class IIa, Level A) [6, 7]. Exercise capacity, measured by VO2-peak, is an independent predictor of all-cause and cardiovascular mortality in patients with CAD [8, 9]. Diabetic patients are known to be at higher risk for CAD, with a worse prognosis after a myocardial infarction compared to non-diabetic patients [10, 11]. Previous studies have shown that CR is less effective in these patients, probably due to impaired glycemic control [12]. Less is known about the value of impaired glucose tolerance (IGT) as a predictor of cardiovascular events in the long-term, however this condition seems to be associated with lower functional recovery [13, 14]. Recently, a positive association between IGT and left ventricular diastolic dysfunction was found in middle-age adults without left ventricular systolic impairment or valvular disease, even after correction for confounding factors [15]. The cardiopulmonary exercise testing (CPET) is commonly performed in patients with CAD to identify post-infarct residual ischemia and to monitor the progress of CR [16, 17]. The aim of the present study is to determine whether CR had a positive effect on exercise capacity and risk factor control in IGT and diabetic patients with CAD.

Methods

One hundred and seventy-one consecutive patients referred to Cardiocentro Ticino (Lugano, Switzerland) for CR, from January 2014 to June 2015, were enrolled in the study. Patients with severe renal failure (as defined by RIFLE classification — Risk, Injury, Failure, Loss of kidney function and End-stage renal disease based on creatinine clearance and urinary output) [18], severe peripheral arterial disease, severe respiratory disease or those simply unable to perform exercise training were excluded. Diabetes was diagnosed by plasma fasting glucose > 126 mg/dL (i.e. > 7.0 mmol/L) or by glycated hemoglobin (HbA1c) > 6.5%. A tri-weekly 2-h session of a comprehensive multidisciplinary CR program began on hemodynamically stable patients and continued for 3 months. The CR team consisted of physiotherapists, psychologists, nutritionists and an experienced cardiologist in cardiovascular rehabilitation. Each session included one or more group-based therapies, such as education about cardiovascular risk factors, dietary suggestions, and physiotherapy as well as exercise and stress management. Exercise sessions of aerobic exercise lasting 30 min, including a warm-up and a cool-down activity. The intensity of exercise was prescribed individually, based on a target heart rate < 85% of the theoretical threshold. Demographic information, anthropometric parameters, medical history, ACS type, cardiovascular risk factors, medications as well as laboratory values were collected at baseline and after completing the CR program (at least > 75% of sessions). A CPET was performed at baseline and at the end of the CR program and was supervised by an experienced cardiologist. This ergometric CPET was conducted with variable work loads of 10 to 25 Watts every 1 or 2 min (incremental protocol), according to a patient's individual functional autonomy. A measurement of patient cardiopulmonary function, such as maximal metabolic equivalents (METs), peak workload and maximal oxygen consumption (VO2-peak), were collected at baseline and at the end of the CR program.

Statistical analysis

Variables were expressed as means ± standard deviation or percentage as appropriate. Comparisons between groups were performed using the two-tailed Student t-test or χ^2 test as appropriate. Correlation coefficients were determined by linear regression analysis and statistical significance was determined with the Fisher and Yates test. Multivariable analyses were performed by stepwise linear regression or by stepwise logistic regression as appropriate. A p-value < 0.05 was considered to be statistically significant. Statistical analysis was performed using the SPSS software (SPSS 22.0 Inc., Chicago IL, USA).

Table 1. Main characteristics of cardiac rehabilitation (CR) patients according to glycemic status.

	Euglycemic (glycemic < 5.6 mmol/L) (n = 88)	IGT (glycemic 5.6–7.0 mmol/L) (n = 59)	Diabetics (glycemic > 7.0 mmol/L) (n = 24)
Age	60,45	63,35	69,30
Male	53	66	24
Familial history of CHD	25	23	4
Hypertension	32	42	20
Dyslipidemia	36	40	11
Diabetes	1	12	21
Smoking	35	38	6
Statin therapy	56	61	21
ACEI	40	41	19
Beta-blockers	59	68	17
Acetylsalicylic acid	64	68	24
Stable angina	28	20	9
Unstable angina	3	2	0
NSTEMI	18	4	4
STEMI	25	22	9
PTCA	55	40	13
CABG (also previous)	23	12	12
Waist > 88 or > 102 cm	31	33	17
Weight > 60 or > 70 kg	50	66	23
ΔGlucose	–0.16 ± 0.46 (p = 0.25)	–0.35 ± 0.75 (p = 0.02)	0.52 ± 1.40 (p < 0.05)
ΔHbA1c	0.40 ± 0.97 (p = 0.67)	0.28 ± 0.53 (p = 0.28)	–0.29 ± 1.20 (p = 0.02)

Data are presented as mean ± standard deviation or percentage. ACEI — angiotensin converting enzyme inhibitor; CABG — coronary artery by-pass graft; CHD — chronic heart disease; HbA1c — glycated hemoglobin; IGT — impaired glucose tolerance; NSTEMI — non-ST-segment elevation myocardial infarction; PTCA — percutaneous transluminal coronary angioplasty; STEMI — ST-segment elevation myocardial infarction

Results

Out of 171 patients enrolled in the study, 148 (86.5%) completed the CR program; 87 (50.9%) patients presented ACS in the prior 4 weeks and 108 (63.1%) underwent a percutaneous transluminal coronary angioplasty (PTCA). After 1 week, 23 (13.4%) patients dropped out the CR program and another 4 patients were excluded from the analysis because of attendance of less than 75% of the sessions (less than 28 of the 36 sessions). Out of 144 patients who completed the CR program, 34 (23.6%) patients were already known to have diabetes; 3 (2.1%) patients were newly diagnosed. Patients with a plasma fasting glucose between 100 and 126 mg/dL (i.e. 5.56 mmol/L and 7.0 mmol/L), independent of their history, were classified as IGT patients; of these 47 (32.6%) were newly diagnosed. The baseline characteristics of the 171 patients, divided in three groups according to their baseline fasting glucose and enrolled in the study are summarized in Table 1.

Effects on exercise capacity based on glucose control

Exercise capacity pre- and post-CR expressed by CPET parameters is summarized in Table 2. All groups showed significant intra-group improvement (Fig. 1) considering workload peak and VO2--peak (except IGT patients). Euglycemic patients benefited the most in terms of exercise capacity improvement (5.7 ± 1.4 to 6.6 ± 1.8 METs, p = 0.018). IGT patients presented a lower functional capacity recovery when compared to euglycemic patients (5.9 ± 1.9 to 6.3 ± 1.8 METs, p = 0.413) as well as diabetic patients (4.8 ± 0.8 to 4.9 ± 1.4, p = 0.072).

A significant improvement in VO2-peak after completing CR was found in euglycemic patients (VO2-peak from 19.3 ± 5.3 to 22.5 ± 5.9 mL/min/kg, p = 0.003) and also in this case, IGT patients showed less benefit compared to euglycemic patients (VO2-peak from 20.2 ± 6.4 to 21.5 ± 7.0 mL/min/kg, p = 0.42). Diabetic patients presented only a positive trend in VO2-peak compared to IGT

Table 2. Cardiopulmonary test values pre- and post-cardiac rehabilitation (CR).

	Euglycemic (< 5.6) (n = 63)	IGT (5.6–7.0) (n=66)	Diabetics (> 7.0) (n = 19)	P
Watt pre-CR	128.5 ± 41.2	128.4 ± 40.0	104.7 ± 38.2	**0.02**
Watt post-CR	137.4 ± 44.0	142.1 ± 46.1	116.1 ± 41.3	0.08
METs pre-CR	5.7 ± 1.4	5.9 ± 1.9	4.8 ± 0.8	**0.03**
METs post-CR	6.6 ± 1.8	6.3 ± 1.8	4.9 ± 1.4	**0.01**
VO2-peak pre-CR	19.3 ± 5.3	20.1 ± 6.3	16.9 ± 3.8	0.07
VO2-peak post-CR	22.5 ± 5.9	21.5 ± 7.0	18.0 ± 4.4	**< 0.05**
VO2 threshold pre-CR	13.9 ± 4.2	14.7 ± 4.3	12.3 ± 2.5	0.11
VO2 threshold post-CR	16.0 ± 4.6	16.3 ± 4.6	13.7 ± 3.9	0.05
O2 beat pre-CR	12.3 ± 3.1	13.0 ± 3.5	11.6 ± 2.3	0.35
O2 beat post-CR	13.1 ± 3.4	13.5 ± 3.7	11.9 ± 2.9	0.19
Breath reserve pre-CR	40.8 ± 15.9	38.1 ± 15.3	37.0 ± 13.5	0.33
Breath reserve post-CR	37.9 ± 17.1	37.0 ± 14.9	33.4 ± 14.6	0.31

Data are presented as mean ± standard deviation. Statistical significance is shown for euglycemic patients vs. diabetics. IGT — impaired glucose tolerance; METs — metabolic equivalents; VO2 — oxygen volume

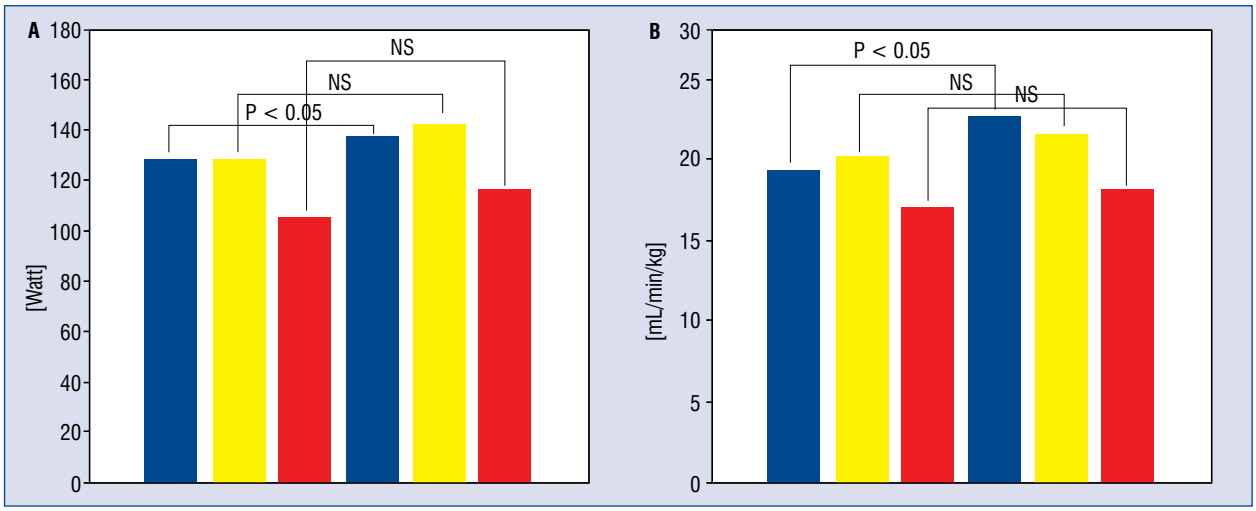

Figure 1. Peak workload and VO2-peak improvement; **A.** Peak workload comparison between euglycemic (blue bars), impaired glucose tolerance (IGT; yellow bars) and diabetic patients (red bars); **B.** VO2-peak comparison between euglycemic (blue bars), IGT (yellow bars) and diabetic patients (red bars); NS — not significant.

(VO2-peak 17.0 ± 3.8 mL/min/kg vs. 18.1 ± 4.4 mL/min/kg, p = 0.056). IGT patients presented the most significant benefit in terms of fasting glucose reduction, compared to diabetic patients (plasma fasting glucose 6.5 ± 0.5 mmol/L to 6.2 ± ± 0.9 mmol/L vs. 8.1 ± 1.8 mmol/L to 8.2 ± ± 1.9 mmol/L, p = 0.002). Diabetic patients, on the other hand, showed a more significant reduction of HbA1c levels compared to IGT patients (HbA1c 7.7 ± 1.1% to 7.5 ± 1.2% vs. 5.6 ± 0.4% to 6.0 ± 0.5%, p = 0.002). Finally, a trend showing an inverse correlation was found between baseline fasting glucose levels and ΔVO2-peak (ΔVO2--peak = 6.419925–0.721243*fasting glucose, p = 0.11, Fig. 2).

Discussion

In this study, results of a comprehensive CR program for CAD patients from a single center experience are presented (Cardiocentro Ticino, Lugano, Switzerland). In the current population, 13.4% of patients quit the CR program after 1 week. This dropout rate is in line with the data previously

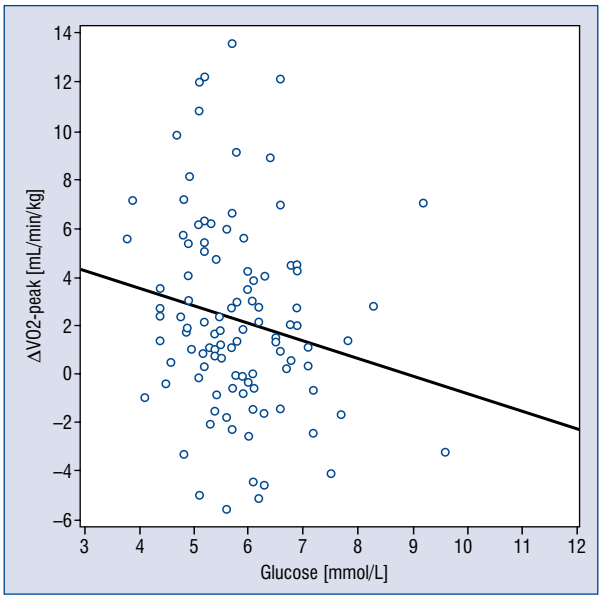

Figure 2. Linear regression, showing an inverse correlation between fasting glucose and VO2-peak improvement, suggesting that response to cardiac rehabilitation may be impaired by poor glycemic control.

reported in the literature [19]. In a big prospective study, including more than 25,000 patients with at least one vessel CAD, diabetic patients were more likely to leave the CR program (odds ratio [OR] 0.65, 95% confidence interval [CI] 0.59–0.72), and, despite being less referred, women experienced a greater relative mortality benefit compared to men [20].

Effects of CR programs on cardiovascular risk factors

Exercise capacity measured by VO2-peak represents a strong predictor of survival in patients with CAD and is positively related to improvement in terms of morbidity [21].

High-intensity interval training protocols have been developed and have been shown to lead to a significant increase in functional capacity compared to moderate continuous training [22]. International Guidelines recommend CR programs including a multimodal behavioral intervention for all patients with established CAD [6, 7].

Exercise is associated with improvements of typical cardiovascular risk factor control such as obesity, diabetes mellitus and hypertension [23]. In the present population, a reduction in weight as well as in waist circumference in all patients was found, independently from glycemic status, although these results were not statistically significant as reported in other previous studies published [24]. Moreover, CR is associated with an increase of muscular mass; therefore, weight loss may not reflect by itself a reduction in cardiovascular risk. An increase in oxygen peak consumption or improvement in glycemic control thus represent more useful indicators.

Effects of CR programs based on glycemic status

The combination of aerobic and resistance training has been shown to be highly effective in reducing cardiovascular risk factors in patients with type 2 diabetes mellitus and is currently recommended by the American College of Sports Medicine and American Heart Association [25, 26]. In the analyses, it was found that IGT patients presented a more significant reduction in plasma fasting glucose compared to diabetic patients. On the other hand, diabetic patients showed a more significant reduction of HbA1c levels, compared to IGT patients. Based on these results, it can be extrapolated that these patients could benefit, in terms of glycemic control, from a longer CR program.

The role of CR as long-term therapy to reduce cardiovascular risk factors after ACS is well established. In a prospective study including 846 patients treated with aorto-coronary by-pass, CR attendance was associated with a significant reduction of 10-year all-cause mortality and CR program completion was the most important indicator for survival [27]. However, no differences in mortality according to glycemic status were found.

In *in vitro* studies, hyperglycemia has been shown to lead to oxidative stress and thus, indirectly, to increase myocyte apoptosis, both in chronic and in acute settings [28, 29]. In the DARE study, a prospective multicenter study, 64 patients with diabetes mellitus type 2 were enrolled in a CR program after ACS. Patients were randomized according to baseline diabetes therapy; patients with better glycemic control, as measured by fructosamine levels, a parameter of short-term glycemic control, showed higher values of VO2-peak at the end of CR [19]. In another prospective study including 682 patients undergoing CR after ACS, diabetic subjects presented a lower functional capacity at baseline compared to non-diabetics. Nevertheless, diabetics patients presented a significant improvement, expressed in METs and exercise duration, similar to those achieved by non-diabetic patients [30]. These findings were confirmed in another

study including heart failure patients [31]. In the current study, it was also found that patients with diabetes have a lower functional capacity at baseline, with an improvement in functional capacity, expressed in terms of both higher peak workload (METs) and VO2-peak values at the end of the CR program when compared to IGT patients. Euglycemic patients, on the contrary, significantly improved both these parameters compared to diabetic patients.

Data from the Italian SurveY on carDiac rEhabilitation (ISYDE-2008) including 2281 patients referred to CR showed that patients with diabetes had more comorbidities and 23% of them were not able to perform any physical performance testing at all. The authors concluded that this finding might have prognostic relevance. A bias in the study involving diabetic patients undergoing CR has thus to be considered, as these patients may have been directly excluded from enrollment in CR programs [32].

In the present study, euglycemic patients benefited the most from the CR program. IGT patients, however, presented a significant improvement of glycemic control compared to diabetic patients in terms of plasma fasting glucose. Diabetic patients, on the other hand, showed a statistically significant reduction of HbA1c. Taken together, these data suggest that improvement in glycemic control during CR may contribute to optimize functional recovery expressed in terms of workload- and VO2--peak, independently from other factors. These improvements are probably due to CR itself, and were independent of underlying therapy for diabetes. Several studies, however, failed to demonstrate the effectiveness of CR in diabetic patients [33, 34], although, according to some other authors, CR should be effective for these patients as well [35]. However, the discrepancies in these studies may be related to the heterogeneity of patients considered. In the current study, it was found that fasting glucose at baseline inversely correlated with VO2-peak improvement and this finding is in line with previously published data [12, 36]. Poor glycemic control seems to have unfavorable effects on cardiomyocytes and muscular cells, promoting overproduction of reactive oxygen species, alterations of myocardial endo-plasmatic reticulum, dysfunction of calcium metabolism and impairment of mitochondria metabolism [29, 37–39]. On the other hand, good glycemic control during CR may improve the VO2-peak [17] and may play a key role for a better long-term prognosis as well.

Limitations of the study

The retrospective analysis, as well as the lack of a control group, represent a limitation of this study, that is also burdened by a small number of patients, all Caucasian. Larger prospective studies are needed to better clarify the role of CR in diabetic patients.

Conclusions

This single-center experience showed how a multidisciplinary CR program provides better outcomes in terms of exercise capacity for euglycemic patients compared to IGT and diabetics patients. These latter patients could benefit from a longer CR program, overall in terms of glycemic control, independently from hypoglycemic therapies. The efficacy of CR in diabetic patients needs to be clarified in larger and prospective studies.

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Conflict of interest: None declared

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Stress perfusion cardiovascular magnetic resonance and serial fractional flow reserve assessment of the left anterior descending artery in patients undergoing right coronary artery chronic total occlusion revascularization

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Abstract

Background: *Fractional flow reserve (FFR) assessment of remote arteries, in the context of a bystander chronic total occlusion (CTO), can lead to false positive results. Adenosine stress cardiovascular magnetic resonance (CMR) evaluates perfusion defects across the entire myocardium and may therefore be a reliable tool in the work-up of remote lesions in CTO patients. The IMPACT-CTO study investigated donor artery invasive physiology before, immediately post, and at 4 months following right coronary artery (RCA) CTO percutaneous coronary intervention (PCI). The aim of this subanalysis was to assess the concordance between baseline perfusion CMR and serial FFR evaluation of left anterior descending artery (LAD) ischemia in patients from the IMPACT-CTO study.*

Methods: *Baseline adenosine stress CMR examinations from 26 patients were analyzed for qualitative evidence of LAD ischemia. The results were correlated with the serial LAD FFR measurements.*

Results: *The present findings demonstrated that before RCA CTO PCI, there was 62% agreement between perfusion CMR and FFR (ischemic threshold ≤ 0.8) in the assessment of LAD ischemia (k = 0.29; fair concordance). At 4 months after revascularization, there was 77% agreement (k = 0.52; moderate concordance) between the index CMR assessment of LAD ischemia and the follow-up LAD FFR. Concordance was improved at a LAD FFR ischemic threshold of ≤ 0.75.*

Conclusions: *In this hypothesis generating study, baseline CMR assessment of LAD ischemia correlated better with the 4 months LAD FFR data (threshold ≤ 0.8) as compared to the FFR measurements taken prior to RCA CTO revascularization.* (Cardiol J 2022; 29, 1: 80–87)

Key words: chronic total occlusion, stress perfusion cardiovascular magnetic resonance, percutaneous coronary intervention

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Introduction

Stress perfusion cardiovascular magnetic resonance (CMR) and fractional flow reserve (FFR) are two frequently performed investigations in patients with suspected myocardial ischemia. FFR is the current gold standard for invasive functional assessment of coronary artery disease of intermediate severity and numerous randomized control trials have highlighted its prognostic value [1–3]. Furthermore, research has shown that perfusion CMR can accurately diagnose flow-limiting lesions as established by FFR [4–6].

Multiple studies have revealed that FFR measured in collateral donor vessels, in the presence of a chronic total occlusion (CTO), will increase after percutaneous revascularisation of the CTO [7–9]. This has important clinical implications; in the recent IMPACT-CTO study an increase in the predominant donor vessel FFR at 4 months following right coronary artery (RCA) CTO percutaneous coronary intervention (PCI) led to a functional reclassification in 18% of lesions at follow-up [7]. Thus, the ability of FFR to identify ischemia in a remote artery territory prior to revascularization of a CTO may not be robust.

Stress perfusion CMR has potential advantages in patients with multivessel disease in the presence of a CTO. CMR documents ischemia at the segmental myocardial level, in contrast to FFR which determines ischemia in a vascular territory. In the presence of a CTO, FFR in a donor artery is influenced not only by the degree of stenosis within the vessel, but also by the additional territory supplied by donor vessel collaterals to the CTO region. The resultant increase in flow and size of myocardial bed leads to a decrease in FFR and potentially a false positive result [8]. This raises the possibility that CMR may be a more accurate method of identifying ischemia in remote territories, which in turn could improve decision making and outcomes in patients with multivessel disease in the presence of a CTO.

In the present study an analysis was performed of patients enrolled in the IMPACT-CTO study to investigate the correlation between baseline stress perfusion CMR and serial FFR measurements of left anterior descending artery (LAD) remote territory ischemia, taken at baseline in the presence of an RCA CTO, and at 4 months after CTO PCI.

Methods

The full methodology and results for the IMPACT-CTO study (NCT02643940 clinical trials.gov number) had been reported previously [7]. In brief, 40 consecutive patients with an RCA CTO scheduled for PCI were recruited between October 2015 and November 2016. Inclusion criteria included symptomatic stable angina, RCA total occlusion of ≥ 3 months duration, evidence of myocardial viability ± ischemia on non-invasive testing, and visible collateral supply from a contralateral donor vessel. Myocardial viability on CMR was defined as < 50% of left ventricular wall hyperenhancement during delayed gadolinium imaging. Exclusion criteria included prior coronary artery bypass grafting, > 1 CTO vessel, and left main stem disease. The study was approved by the regional ethics committee (15/EE/0269) and all patients gave written informed consent. CTO PCI was performed with conventional techniques by experienced operators. FFR assessment of remote vessels was performed using a pressure wire (Philips Volcano Corporation, San Diego, California) before, immediately after, and at 4 months following RCA CTO PCI. Hyperemia was attained with an intravenous adenosine infusion administered via a femoral vein at a dose of 140 mcg/kg/min. Intracoronary nitroglycerine was administered before the physiological measurements were acquired. The pressure wire was normalized at the end of the guide catheter and passed to the distal aspect of the remote vessel. Two FFR ischemic thresholds of ≤ 0.8 and ≤ 0.75 were used in this sub analysis.

CMR protocol

Baseline perfusion CMR examinations were undertaken on a subset of patients in the IMPACT--CTO study in a 1.5-T scanner (Siemens MAGNETOM Aera). Standard cine steady-state-free--processing images were collected in three long axis views and multiple short axis slices. Perfusion data was acquired after a 3–4 min adenosine infusion (140 μg–210 μg/kg/min) and subsequent gadolinium-based contrast agent injection (0.1 mmol/ /kg at 6 mL/s). Three slices (basal, mid ventricular, and apical) were then obtained during the first pass using a TurboFLASH T1 weighted gradient echo sequence. Rest perfusion images were acquired after a period of 10 min and a second bolus of gadolinium contrast agent (0.1 mmol/kg at 6 mL/s) was administered for the delayed enhancement imaging (assessed at an additional 7 min interval).

CMR analysis

The stress CMR data was analyzed by two experienced readers (SG and JND) blinded to the left coronary anatomy and background history. The myocardium was divided using a 16-segment model (American Heart Association 17-segment model minus the apical cap). For the main analysis, the

LAD was allocated into segments 1, 2, 7, 8, 13, and 14. The RCA was assigned segments 3, 4, 9, 10, and 15 (all patients were RCA dominant) and the left circumflex artery was assigned segments 5, 6, 11, 12, and 16. Visual assessment of LAD ischemia was determined by consensus agreement by the imaging consultants. Inducible perfusion defects were defined as delayed entry of contrast (persisting for more than 5 heart beats) in the absence of a scar. The cine sequences and delayed enhancement images were assessed simultaneously in order to evaluate for regional wall motion abnormalities and infarcted myocardium. A Siemens Syngo.via workstation was used for all analysis.

Reassignment of coronary territories

To assess the potential impact of variable coronary anatomy, one experienced interventional cardiologist (JRD) reviewed all angiographic data included in the sub analysis. Each myocardial segment subsequently reassigned (from the 16-segment model) to the specific coronary artery subtending that territory. The reassignment of perfusion territories was blinded.

Statistical analysis

Continuous data is presented as means ± standard deviation. Categorical data is expressed as percentages. Percentage agreement and the kappa statistic was used to assess concordance between the perfusion CMR and FFR results (a kappa statistic of +1 signifying perfect agreement and a kappa statistic of –1 signifying full disagreement). Statistical analysis was performed using GraphPad.

Results

Twenty-six patients had baseline perfusion CMR testing and follow up remote artery FFR measurements at 4 months. All of these individuals were included in the final analysis. Average age was 62 ± 9.8 years, 89% were male, 19% had diabetes mellitus, and the mean LAD stenosis by quantitative coronary angiography (QCA) was 41% ± 11.1%. There was no significant difference in the hemodynamic parameters (central venous pressure, mean arterial pressure, and heart rate) during FFR assessment at baseline and follow-up. Full demographic data is presented in Table 1.

Table 1. Baseline demographic and angiographic data.

	N (%) or mean ± SD
Demographic (n = 26)	
Male	23 (85%)
Age [years]	62 ± 9.8
Previous MI	17 (65%)
Previous PCI	10 (38.5%)
Hypertension	17 (65.4%)
Hypercholesterolemia	20 (76.9%)
Diabetes mellitus	5 (19.2%)
Current smoker	5 (19.2%)
Angina duration [months]	37.15 ± 52.48
Angina CCS class (1/2/3/4)	3 (12%)/10 (38%)/ /13 (50%)/0 (0%)
Estimated CTO duration [weeks]	224.38 ± 392.16
Angiographic details	
RCA CTO	26 (100%)
LAD stenosis on QCA [%]	40.91 ± 11.07

SD — standard deviation; MI — myocardial infarction; PCI — percutaneous coronary intervention; CCS — Canadian Cardiovascular Society; CTO — chronic total occlusion; RCA — right coronary artery; LAD — left anterior descending artery; QCA — quantitative coronary angiography

LAD FFR analysis

Sixteen (62%) patients had a positive LAD FFR (≤ 0.8) at baseline, 16 (62%) patients had positive LAD FFR (≤ 0.8) immediately after RCA CTO PCI, and 12 (46%) patients had a positive LAD FFR (≤ 0.8) at 4-month follow-up.

Perfusion CMR analysis

Perfusion CMR demonstrated RCA territory ischemia in 25 (96%) patients and LAD ischemia in 8 (31%) patients.

CMR and FFR concordance in the assessment of LAD ischemia

There was 62% agreement between baseline CMR and FFR (cut off ≤ 0.8) in the assessment of LAD ischemia (k = 0.29; fair concordance) prior to RCA CTO PCI. 4 months after revascularization, there was 77% agreement (k = 0.52; moderate concordance) between the baseline CMR and the follow-up FFR (cut off ≤ 0.8) assessment of LAD ischemia. In the cases of FFR and CMR discordance was at 4 months; 1 patient was CMR positive and FFR negative for LAD ischemia and 5 individuals were FFR positive and CMR negative for LAD ischemia (Table 2A).

5/26 (19%) of patients had a positive LAD FFR (≤ 0.80) prior to revascularisation and a negative LAD FFR (> 0.8) at 4 months. Perfusion CMR was negative for LAD ischemia in all of these

Table 2. A. Concordance between baseline perfusion cardiovascular magnetic resonance (CMR) and serial fractional flow reserve (FFR) measurements (at an ischemic threshold of ≤ 0.80); **B.** Concordance between baseline perfusion CMR and serial FFR measurements (at an ischemic threshold of ≤ 0.75). The results were not affected by reassignment of coronary territories following blinded angiographic review.

A	FFR results (threshold of ≤ 0.80)			
	Prior to RCA CTO PCI		4 months following RCA CTO PCI	
CMR result	LAD FFR negative	LAD FFR positive	LAD FFR negative	LAD FFR positive
Negative for LAD ischemia	9	9	13	5
Positive for LAD ischemia	1	7	1	7
B	**FFR results (threshold of ≤ 0.75)**			
	Prior to RCA CTO PCI		4 months following RCA CTO PCI	
CMR result	LAD FFR negative	LAD FFR positive	LAD FFR negative	LAD FFR positive
Negative for LAD ischemia	15	3	15	3
Positive for LAD ischemia	1	7	2	6

RCA — right coronary artery; CTO — chronic total occlusion; PCI — percutaneous coronary intervention; LAD — left anterior descending artery

studies. Examples of concordant and discordant assessments of myocardial ischemia are shown in Figures 1 and 2.

At a lower FFR ischemic threshold of ≤ 0.75, there was 85% agreement between CMR and FFR in the assessment of LAD ischemia prior to RCA CTO PCI (k = 0.66; good concordance). At 4 months following RCA CTO revascularization, there was 81% agreement (k = 0.56; moderate concordance) between the baseline CMR and follow up FFR measurement of LAD ischemia at that decreased cut off (Table 2B).

In 22 patients, the LAD was the predominant donor vessel to the RCA CTO territory. In these individuals, there was 59% agreement between CMR and FFR (cut off ≤ 0.8) in the evaluation of LAD ischemia prior to RCA CTO PCI (k = 0.26; fair concordance). At 4 months following RCA revascularization, there was 72% agreement (k = 0.46; moderate concordance) between the baseline CMR and the follow up FFR (cut off ≤ 0.8) assessment of LAD ischemia. At a lower FFR threshold of ≤ 0.75, there was 82% agreement between FFR and CMR results (k = 0.61; good concordance) prior to RCA CTO PCI. At 4 months after revascularization, there was 77% agreement (k = 0.50; moderate concordance) between the baseline CMR and follow up FFR results at this reduced threshold.

Reassignment of coronary territories

Concordance between CMR and FFR was not affected by the reassignment of coronary territories following blinded angiographic review (Table 2A, B).

Collateral vessel regression

Twenty-two (85%) patients in the sub analysis had evidence of full regression of their collateral vessels at follow up. One of the four patients who had persisting collateral circulation had discordant results at four months (LAD FFR 0.62 and CMR negative for LAD ischemia).

Discussion

The major findings of this study are:

— There appears to be only fair concordance between perfusion CMR and FFR (ischemic threshold ≤ 0.8) in the assessment of LAD ischemia prior to RCA CTO revascularization;

— Baseline perfusion CMR appears to correlate better with the FFR assessment (cut off ≤ 0.8) of LAD ischemia at 4 months post RCA CTO PCI as compared to before revascularization. This result appears to be due to the ability of a negative baseline CMR to identify patients with negative LAD FFR measurements at 4-month follow-up;

— Concordance in the assessment of LAD ischemia between perfusion CMR and pre-CTO PCI FFR appears to be improved at a lower ischemic threshold (cut off ≤ 0.75).

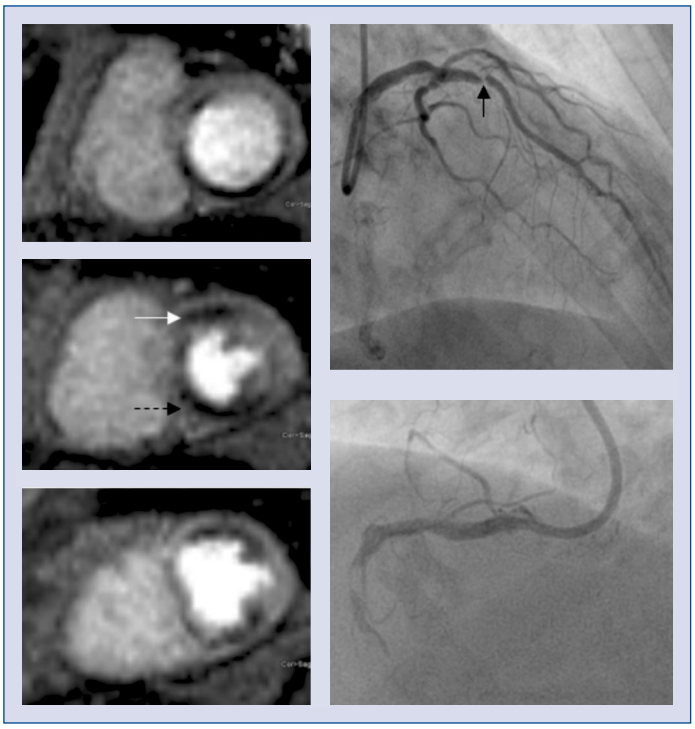

Figure 1. Concordant stress perfusion cardiovascular magnetic resonance (CMR) and fractional flow reserve (FFR) results. CMR imaging (left panel) demonstrating a perfusion defect in the left anterior descending (LAD) artery (e.g. white arrow) and right coronary artery (RCA; e.g. dashed arrow) territories. Coronary angiogram (right panel) demonstrating concordant findings with a severe LAD lesion (FFR 0.58 at baseline and 0.33 at 4 months; black arrow) and an occluded RCA.

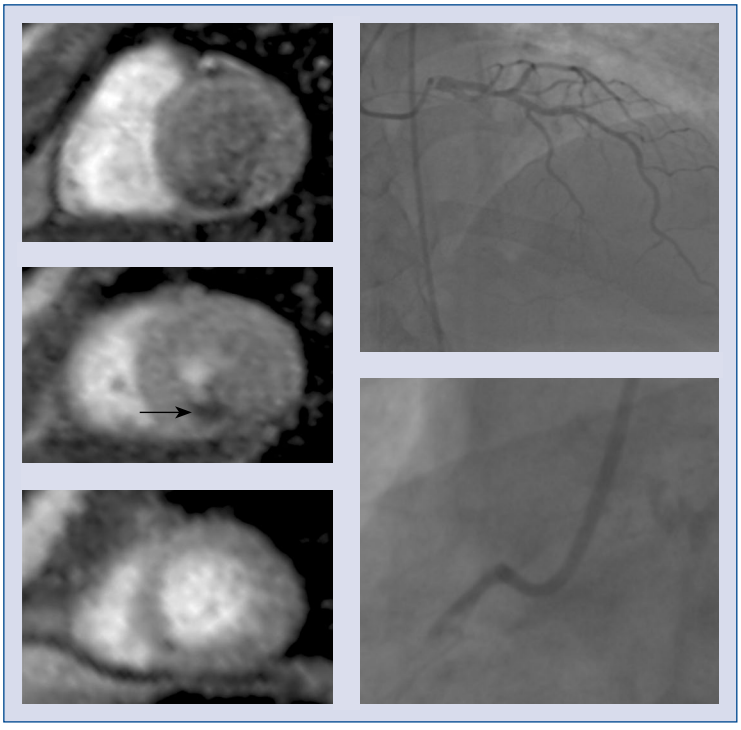

Figure 2. Discordant stress perfusion cardiovascular magnetic resonance (CMR) and baseline fractional flow reserve (FFR) result. CMR imaging (left panel) demonstrating a perfusion defect in the right coronary artery (RCA) territory (e.g. black arrow). Coronary angiogram (right panel) demonstrating discordant findings with an occluded RCA and a left anterior descending artery with an FFR of 0.78 at baseline and 0.82 at 4 months following RCA percutaneous intervention.

Correlation between CMR and FFR in assessment of LAD ischemia in the context of an RCA CTO

In this sub analysis, there is only fair concordance between perfusion CMR and FFR assessment of LAD ischemia prior to RCA CTO PCI (using an FFR threshold of ≤ 0.80). This result does not appear to be greatly affected by stratifying for the donor vessel or by the standard assignment of perfusion territories (i.e. the American Heart Association 17-segment model minus the apical cap). The majority of the discordance was due to patients with positive LAD FFR lesions and negative perfusion CMR scans (for LAD ischemia).

These results are similar to prospective studies assessing CMR and FFR in the assessment of multivessel disease (MVD). Hussain et al. [10] compared the diagnostic accuracy of perfusion CMR and FFR in patients with 2- and 3-vessel disease. They found fair concordance (at a per vessel basis analysis) between the two modalities and demonstrated that CMR either underestimated, or FFR overestimated the number of ischaemic territories in 33% of cases [10]. A further study by Nakamori et al. [11] again assessed the concordance of myocardial perfusion CMR to FFR in patients with both single, and MVD. In their study, visual assessment of ischemia by CMR (at a per vessel level analysis) had a sensitivity of 64% and a specificity of 79% against FFR in 2- or 3-vessel disease [11]. In contrast, in patients with single vessel disease, sensitivity of CMR was 83% and specificity was 95% (as compared to FFR) [11].

The etiology of the discordance found in the present sub analysis is likely multifactorial but will, in part, be due to inherent limitations of both modalities in individuals with a CTO. FFR influenced by myocardial mass subtended by the vessel being interrogated [12]. In patients with a collateralized CTO, coronary arteries not only supply their own territory, but also the myocardium of the occluded vessel. As such, the use of fractional flow to evaluate remote artery ischemia in such patients could have limitations and may lead to false positive results.

Stress perfusion CMR imaging could also have limitations in patients with MVD. Firstly, visual assessment of ischemia may be liable the same errors encountered with myocardial perfusion imaging (with single-photon emission computed tomography) in MVD. Myocardial perfusion imaging (MPI) relies on relative flow heterogeneity and as such, can encounter problems with 2- or 3-vessel disease [13]. In these cases, MPI identifies the territories subtended by the most severe stenoses and has the potential to disregard perfusion defects in other myocardial segments [13]. Conversely, CMR has superior spatial resolution (i.e. can distinguish between subendocardial and transmural perfusion deficits) and therefore false negative results may potentially be avoided in MVD [11]. Indeed, sub analysis in the CE-MARC study revealed that triple-vessel disease was not significantly associated with false negative perfusion CMR results [14].

In the case where FFR was negative and CMR was positive for LAD ischemia, there was no significant epicardial stenosis on quantitative coronary angiography. The CMR result may therefore have reflected microvascular ischemia and indeed, it is known that microvascular disease can alter the ability of FFR to assess the significance of epicardial disease [15].

Concordance of baseline CMR and serial FFR measurements in patients undergoing RCA CTO PCI; ischemic FFR threshold ≤ 0.8

In this small hypothesis generating study, baseline perfusion CMR appears to correlate better with FFR in the assessment of LAD ischemia at 4 months post RCA CTO PCI as compared to before revascularization. This result appears to be driven by the ability of a negative baseline CMR to identify patients with negative LAD FFR measurements at 4-month follow-up.

These are interesting findings as the IMPACT--CTO study concluded that interpretation of baseline FFR measurements in vessels providing major collaterals to a CTO should be made cautiously [7]. In particular, when their FFR values were close to the ischemic cut off, the indices only became reliable after collateral vessel regression (i.e. at 4 months post PCI in the IMPACT-CTO study) [7]. In clinical practice however, revascularization decisions are often guided by index invasive coronary physiology of contralateral arteries in CTO patients. A 'gold standard' test would correctly identify significant epicardial stenoses independent of the altered coronary physiology of a collateralized CTO. The current sub analysis suggests that baseline CMR improved correlation with invasive data acquired at 4 months and as such, could act as a reliable tool in the evaluation of remote artery lesions prior to CTO PCI.

A recent study by Bucciarelli-Ducci et al. [16] assessed the use of CMR in the management of patients with a coronary CTO. As part of their study, remote territory myocardial perfusion reserve was measured (MPR) before and after CTO PCI (66%

of their study patients had MVD) [16]. At 3-month follow-up, there was no significant change in the remote territory MPR as compared to the assessment prior to CTO revascularization [16]. Another study by Cheng et al. [17] evaluated resting and hyperemic myocardial blood flow (MBF) by CMR in individuals undergoing CTO recanalization. They found that the remote segment MBF (resting or hyperemic) did not significantly rise at 6 months following CTO PCI as compared with baseline [17]. As with the present results, these studies suggest that CMR may be able to reliably assess the significance of bystander disease in patients with a CTO even prior to CTO revascularization.

It is unlikely that the failure of collateral regression significantly impacted the current results. Ongoing presence of donor vessels arising from the LAD could have affected the LAD FFR. In the present study however, only 4 patients had evidence of ongoing collateral circulation at 4 months. One of these patients had discordant results and this individual had a strongly positive LAD FFR (FFR 0.62) and a negative perfusion CMR for LAD ischemia. As such, it was felt that this was a false negative CMR result and not the consequence of residual LAD supply to the RCA territory.

Concordance of baseline CMR and serial FFR measurements in patients undergoing RCA CTO PCI; ischemic FFR threshold ≤ 0.75

At a lower FFR ischemic threshold of ≤ 0.75, the correlation between the two assessments of LAD ischemia improved. This is in keeping with a prior study which highlighted improved concordance when a reduced ischaemic cut-off for invasive physiological measurements was utilised in MVD [10]. The present results suggest that prior to CTO revascularization, a lower FFR ischemic threshold may be more appropriate in guiding the decision to revascularize the donor vessel.

Limitations of the study

This study has a number of limitations including its small number of subjects. Another main limitation is its design. Although CMR readers were blinded to the left coronary anatomy, they were aware that each patient had an RCA CTO. As such, there was a potential bias towards assessing for inferior ischemia. In addition, undertaking a repeat CMR at 4 months (to mirror the follow-up invasive measurements) would have allowed for a much improved analysis on the use of perfusion CMR in this cohort. Indeed, there are major limitations in comparing baseline CMR scans to FFR data collected 4 months following the index non-invasive test and a PCI procedure. As mentioned above however, a number of studies have performed serial perfusion CMRs in CTO patients [16, 17]. Interestingly, these studies did not find evidence of significant variation in remote territory ischemia following CTO PCI [16, 17]. Therefore, it may be fair to assume that the perfusion CMR appearance in the LAD territory would not have changed on follow-up imaging in the IMPACT-CTO cohort, in the absence of further revascularization. As such, baseline perfusion CMR examinations herein, may be a reliable comparator against the serial FFR measurements.

A further potential limitation is that qualitative assessment of CMR ischemia was performed in the current analysis. This does have the disadvantage of requiring a normal reference area of myocardium for visual comparison. Utilising a semiquantitative, or quantitative, approach to CMR analysis would have potentially provided a more robust assessment of inducible perfusion deficits. Finally, 2-dimensional perfusion CMR (as conducted in the present study) is limited by a lack of total myocardial coverage (e.g. conventionally three non-contiguous short axis myocardial slices, excluding the apical cap) [18]. Three-dimensional perfusion CMR is an exciting area of development which allows for whole-heart coverage and has been shown to have good diagnostic accuracy as compared to FFR [19].

Further studies incorporating all of the above methodological changes would enhance the strength of the ensuing results.

Conclusions

The IMPACT-CTO CMR analysis highlights the potential use of CMR in the work up of patients with borderline LAD lesions and an RCA CTO. Larger prospective studies are needed to assess whether baseline perfusion CMR is able to reliably act as a gatekeeper for revascularization in patients with LAD disease and an RCA CTO.

Conflict of interest: None declared

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Success rate and safety of catheter ablation in preexcitation syndrome: A comparison between adult and pediatric patients

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Abstract

Background: *In contrast to adults, in whom cardiac rhythm disorders are mainly conditioned by coronary artery disease, in children, arrhythmias are most often associated with inherited heart disorders. Catheter ablation (CA) has an important role in the management of cardiac arrhythmias, in adults and children. The aim of the study was to assess and compare the efficacy and safety of CA in children and adults with preexcitation syndrome.*

Methods: *The study population comprised 43 adults and 43 children diagnosed with a Wolff-Parkinson-White syndrome (WPW). The mean age of the study population was 41 ± 15 years for adults and 14 ± 2.5 years for children. In all patients, an electrophysiological study and CA were performed. Analysis with respect to the procedure duration, fluoroscopy exposure time, location of accessory pathways (AP), immediate success rate and complications were performed.*

Results: *Electrophysiological study revealed the most frequent presence of left-sided AP (56% in children and 70% in adults). The mean procedure duration was 96 ± 36 min and 106 ± 51 min in children and adults, respectively (p = NS). The mean fluoroscopy duration was 8.5 ± 4.3 min and 5.9 ± 5.8 min in children and adults, respectively p < 0.05. The CA procedure was successful in 40 out of 43 (93%) adults and in 36 out of 43 (83.7%) children (p = NS). In 2 (4%) children minor complications occurred.*

Conclusions: *Ablation in children and adults are equally effective with respect to short-term clinical observation.* (Cardiol J 2022; 29, 1: 88–92)

Key words: catheter ablation, preexcitation syndrome, accessory pathways, arrhythmia, children, adults

Introduction

Catheter ablation (CA) procedure has become a crucial way of treatment for heart rhythm disturbances both in an adult and pediatric populations. Since it was introduced in children at the beginning of the 90s', it has completely changed the approach to a vast majority of arrhythmias, including supraventricular tachycardias due to preexcitation syndrome [1]. Preexcitation syndrome is the most common indication to CA in the pediatric population. However, in many countries, this way of treatment still presents a big challenge due to a lack of centres specialized in CA in children.

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Moreover, many physicians still consider CA as a risky procedure in children. Due to this fact they try to postpone CA, limiting sport participation until they are successfully treated. It may have some deleterious consequences considering both general health and social life for children.

Atrial fibrillation (AF) is the most common arrhythmia in adults however, there is still a considerable group of patients with preexcitation syndrome. AF is considered a major risk factor for sudden cardiac death in adult patients with preexcitation syndrome (Wolff-Parkinson-White syndrome [WPW]). For these reasons, CA has to be considered in patients with WPW before the risk of AF increases.

The aim of the study was to assess and compare the efficacy and safety of CA in children and adults suffering from WPW.

Methods

The retrospective study was performed. The study group comprised 43 consecutive paediatric patients with an average age of 14 ± 2.5 years and 43 consecutive adult patients with an average age of 41 ± 15 years (Table 1). Patients with WPW were referred to electrophysiological study (EPS) and CA between 2016 and 2017. Diagnosis of WPW and the accessory pathways (AP) location were based on 12-lead standard electrocardiogram (ECG) using the Lucas Boersma algorithm before the procedure and confirmed during EPS [2]. In all patients, a morphologically normal heart was confirmed by echocardiography using the Philips iE33 system (Philips Medical Systems, Andover, MA, USA).

EPS and ablation strategy

All adults underwent EPS and CA according to the same scheduled conduct routinely followed in the site as follows. All antiarrhythmic agents were withdrawn at least five half-lives prior to the procedure. Vascular access was gained via femoral veins. Two diagnostic catheters were introduced for the EPS and were placed in the right ventricle and coronary sinus. Programmed atrial and ventricular stimulation was performed to induce atrioventricular re-entrant tachycardia (AVRT) and to measure the effective refractory period (ERP) of the AP, which was the longest A1–A2 interval without preexcitation. In patients with left-sided pathways, a transseptal puncture was performed to access the left atrium (LA). After the transseptal puncture, patients were heparinised when LA access was needed (target activated clotting time 300–400 s).

Table 1. Demographic data.

Characteristics	Adults	Pediatric patients
Number of patients	43	43
Female/male	18/25	13/30
Mean age [years]	41 ± 15	14 ± 2.5
Weight [kg]	80 ± 21	32 ± 4.5

The ablation catheters were navigated under fluoroscopic and electroanatomic system guidance (Carto 3, Johnson and Johnson, USA). Catheter ablation followed the diagnostic EPS. Programmed atrial and ventricular stimulation was performed to confirm the diagnosis of WPW, induce AVRT and prove the presence of an additional pathway, as well as to localize the exact location of the accessory pathways, as described in the literature [3]. On three-dimensional (3D) map, directly before ablation, the bundle signal was marked using an ablation catheter.

The following settings were used while delivering radiofrequency energy: irrigated tip ablation — power control mode (temperature limit 48°C, power limit of 30 W; Navistar ThermoCool, Biosense Webster, Diamond Bar, CA, USA). The CA was defined as a successful when 15 min after the procedure, provided no signs of arrhythmia were documented.

Statistical analysis

Results are presented as mean ± standard deviation (SD) and percentages. Demographic, EP, CA procedure and complications were analyzed. The Spearman test was used to calculate correlations. The Fisher exact test was used in the analysis of contingency tables. Significance was taken as being $p < 5\%$. All tests were performed using Statistica 13.2 software.

Bioethics committee

The study was registered in the University Bioethics Committee. Written, informed consent was obtained prior to the procedure from all patients and in the case of children — from the parents and from patients above 15 years of age.

Results

Electrophysiological study

In 24 (56%) of the children and 30 (70%) of the adults, AP was diagnosed on the left side. Left free wall was the most common location, 16 (37%) and

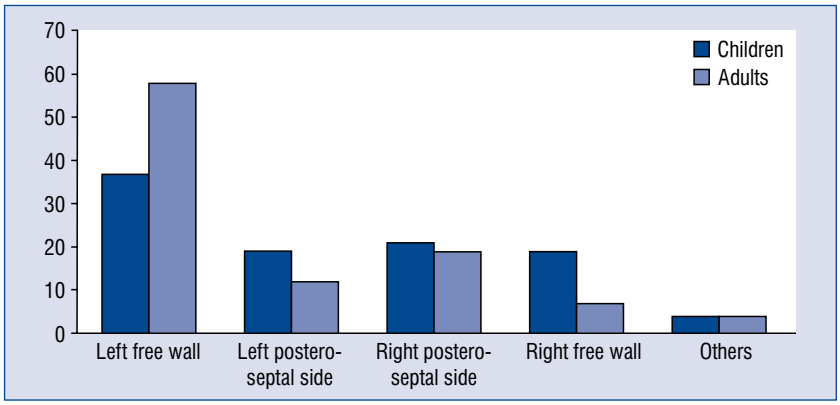

Figure 1. Locations of accessory pathways in children and adults.

Table 2. Procedure data.

Parameter	Adults (n = 43)	Pediatric patients (n = 43)	P
Time of procedure [min]	96 ± 36	106 ± 51	NS
Fluoroscopy time [min]	5.9 ± 5.8	8.5 ± 4.3	< 0.05
Fluoroscopy dose [μGY/cm^2]	12 ± 13	17 ± 11	NS
Transseptal puncture	31 (72.1%)	23 (53.5%)	NS
Complications	0 (0.0%)	2 (4%)	–
Success rate	40 (93%)	36 (83.7%)	NS

25 (58%) in children and in adults, respectively. The AP was located on the left posteroseptal side in 8 (19%) children and 5 (12%) in adults. Transseptal puncture was conducted in all cases when AP was located on the left side. The most frequent location on the right side was the right posteroseptal AP — 9 (21%) in children and 8 (19%) in adults. Right side free wall AP was diagnosed in 8 (19%) children and 3 (7%) in adults. Two children and two adults were diagnosed with a right anteroseptal location of AP (Fig. 1). The ERP was assessed in both groups. In children, the mean ERP at rest was 275 ± 86.5 ms and in adults, the mean ERP was 250 ± 56.8 ms (p = NS).

Catheter ablation

The mean procedure duration was shorter in children (96 ± 36 min) than in adults (106 ± 51 min) but this difference was not statistically significant (p = NS). The mean fluoroscopy duration in children was statistically significantly longer than in adults and was 8.3 ± 4.3 min vs. 5.9 ± 5.8 min, respectively (p < 0.05). The success rate was satisfactory in both groups. In the pediatric population, 15 min after the procedure, arrhythmia was not documented in 36 out of 43 children (84%) whereas in adults it was 40 out of 43 patients (93%) and this difference was not statistically significant (p = NS; Table 2).

Two pediatric patients had minor complications — one had a first-degree atrioventricular block and the second had a pseudoaneurysm in the location of the catheter. No complications in adults were noted.

Discussion

For a long time now, catheter ablation has been a leading procedure in the treatment of WPW in the adult population. In accordance with its high success and safety rate, it has become to play an important role in the treatment of children [4, 5]. In this study, an experience in the ablation of cardiac arrhythmias in children and adolescents is presented and these data are compared with the data derived from the adult center. The procedures were performed by the same team, at the same time in both populations, which makes the study unique. This allowed us to rule out any trial limitations resulting from an altered approach to the procedure due to individual experience and customs of the team.

In the present study, most of the accessory pathways were located on the left side (53 out of 86 patients), which is in agreement with Di Biase et al. study [6]. They found that the AP was located on the left lateral wall in 50–60%, on the posteroseptal wall in 25–30% and within the right free wall space in 10–21%. As it is well described in current publications, success is higher for left-sided pathways than for any other location. This fact may be explained by better catheter stability and a simpler anatomy of the LA, which facilitates detailed mapping along the mitral valve annulus [7, 8]. The difference in immediate success rate in children and adults in the current study was not statistically significant and came to 83.7% and 93%, respectively. These data are similar to the data given in the literature separately for both populations. According to data in the literature, the immediate success rate in pediatric population ranges from between 87.5% and 97% [3, 4, 7, 9, 10]. In Lee et al. study [11] CA was successful in 93% of adults. The Pediatric Radiofrequency Ablation Registry reported an early success rate at the level of 94.4%, for ablation of accessory pathways in all locations [12, 13].

According to the published data, pharmacological treatment of supraventricular tachycardia (SVT) in the pediatric population appeared effective in about 64% of all the cases, depending on the type of arrhythmia and medication. As it was mentioned above, the CA procedure has a significantly higher success rate than pharmacological treatment [13–16]. In terms of effectiveness, these results emphasize the superiority of ablation over pharmacology.

At a pediatric age, ablation is usually more difficult than in adult patients due to the small body size, different electrical properties of the cardiac conduction system, as well as slightly different relations of anatomical structures of children's hearts. These factors not only make placing the electrodes properly inside the heart more difficult but also increase the possibility of damaging significant heart structures. They also have some impact on judgment of the diagnostic pacing manoeuvre during EPS. Moreover, they explain longer fluoroscopy time during the procedures in the paediatric population. Due to these facts, the use of 3D mapping is a useful tool to consider, especially in the pediatric population. 3D mapping additionally shortens the fluoroscopy time and makes all procedures safer, considering deleterious effect of an X-ray to developing systems and organs in children because of the cumulative risk of radiation. In the documented Center, mean fluoroscopy time was similar to that reported in the literature. According to the Multicentre Pediatric and Congenital EP Quality Initiative (MAP-IT) registry, fluoroscopy time in pediatric ablation has improved over the last 25 years from 47.6 ± 40 min to 7.0 ± 9.2 min ($p < 0.001$) [9], whereas in the current Center it was 8.5 ± 4.3 and 5.9 ± 5.8 min in children and adults, respectively. Therefore, the present study is in accordance with trials when considering trends in fluoroscopy time reduction.

According to the present data, 9% of pediatric patients encompassed minor complications, the most serious of which was a transient first-degree atrioventricular block. According to Lee et al. study [11], it is a common complication. Compared to the present results, in Melo et al. [17] the study procedure-related complications were observed among 12% of children with clinically documented SVT who underwent CA and in 11.7% of pediatric patients in the study conducted by Hafez et al. [5].

To conclude, CA has changed the approach to the management of cardiac arrhythmias due to its better effectiveness than pharmacological treatment. It is also more cost-effective than long-term pharmaceutical treatment [18].

Limitations of the study

The study population was relatively small as it encompassed only patients with WPW.

Conclusions

Ablation in children and adults are equally effective with respect to short-term clinical observation.

Conflict of interest: None declared

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Monotherapy versus combination therapy of statin and renin–angiotensin system inhibitor in ST-segment elevation myocardial infarction

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Abstract

Background: *The beneficial effects of statin and renin–angiotensin system inhibitor (RASI) are well-known. In this retrospective cohort study, 2-year clinical outcomes were compared between monotherapy and combination therapy with statin and RASI in ST-segment elevation myocardial infarction (STEMI) patients after stent implantation.*

Methods: *A total of 17,414 STEMI patients were enrolled and divided into the three groups (group A: 2448 patients, statin alone; group B: 2431 patients, RASI alone; and group C: 12,535 patients, both statin and RASI). The principal clinical endpoint was the occurrence of major adverse cardiac events (MACEs) defined as all-cause death, recurrent myocardial infarction, and any repeat revascularization.*

Results: *After adjustment, the cumulative incidences of MACEs in group A (adjusted hazard ratio [aHR] 1.337; 95% confidence interval [CI] 1.064–1.679; p = 0.013) and in group B (aHR 1.375; 95% CI 1.149–1.646; p = 0.001) were significantly higher than in group C. The cumulative incidence of all-cause death in group A was significantly higher than that in group C (aHR 1.539; 95% CI 1.014––2.336; p = 0.043). The cumulative incidences of any repeat revascularization (aHR 1.317; 95% CI 1.031–1.681; p = 0.028), target lesion vascularization, and target vessel vascularization in group B were significantly higher than in group C.*

Conclusions: *A statin and RASI combination therapy significantly reduced the cumulative incidence of MACEs compared with a monotherapy of these drugs. Moreover, the combination therapy showed a reduced all-cause death rate compared with statin monotherapy, and a decreased repeat revascularization rate compared with RASI monotherapy.* (Cardiol J 2022; 29, 1: 93–104)

Key words: ST-segment elevation myocardial infarction, statin, renin–angiotensin system, long-term outcome

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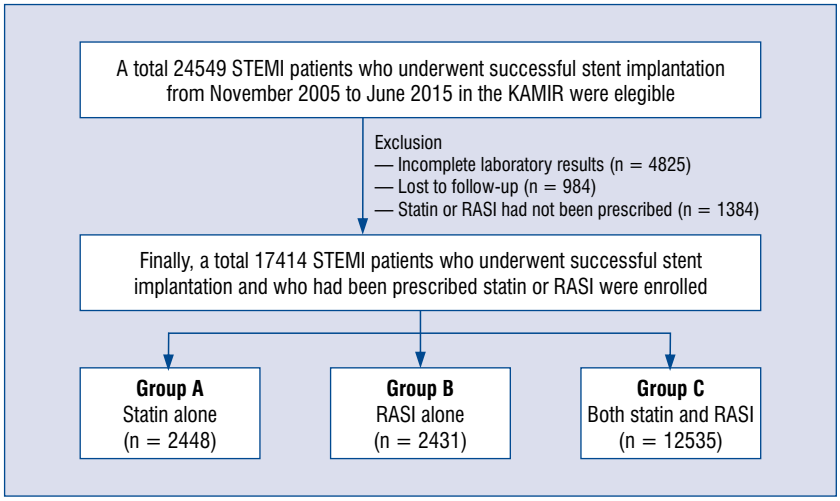

Figure 1. Flow chart; KAMIR — Korea Acute myocardial Infarction Registry; STEMI — ST-segment elevation myocardial infarction; RASI — renin–angiotensin system inhibitor.

Introduction

Through the inhibition of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity, statin plays essential roles in primary and secondary prevention of adverse cardiovascular events [1–3]. The European guidelines recommend starting high-intensity statin therapy as early as possible, unless contraindicated, and maintain it long-term in patients with ST-segment elevation myocardial infarction (STEMI) (Class 1A) [4]. Similarly, the American guidelines recommend the use of early high-intensity statin therapy and should be continued in all STEMI patients (Class 1B) [5]. Renin–angiotensin system inhibitors (RASI) are beneficial for reducing mortality in STEMI patients after percutaneous coronary intervention (PCI) [6], and RASI is recommended in the current guidelines as Class 1A [4, 5]. Even though the beneficial effects of statin and RASI are well-known, results focused on the comparative efficacy of combination therapy of statin and RASI, including an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) and statin, or RASI monotherapy on the occurrence of major adverse cardiac events (MACEs) during a long-term follow-up period in patients with STEMI who underwent successful stent implantation are limited. In this study, we investigated the difference in clinical outcome parameters between this combination therapy and monotherapy in STEMI patients after successful stent implantation, during a 2-year clinical follow-up period.

Methods

Study design and population

The Korea Acute Myocardial Infarction Registry (KAMIR) is a nationwide, prospective, multicenter registry in South Korea, established in November 2005. The KAMIR provides the public and physicians in the "real-world" clinical practice with the demographic characteristic and treatment strategies of the acute myocardial infarction (MI) in Korea [7]. The present study is a non-randomized, multicenter, observational, retrospective cohort study. A total of 24,549 STEMI patients in KAMIR from November 2005 to June 2015 were evaluated. Among them, patients who had the following conditions were excluded: (1) incomplete laboratory results (n = 4825, 19.7%), (2) lost to follow-up (n = 984, 4.0%), (3) statin or RASI had not been prescribed (n = 1384, 5.6%). After exclusion, a total of 17,414 STEMI patients who underwent successful stent implantation and who had been prescribed statin or RASI were enrolled. The patients were classified into group A (2448, 14.1%), group B (2431, 13.9%), and group C (12,535, 72.0%), and received statin alone, RASI alone, or both statin and RASI, respectively, as treatment (Fig. 1). The beneficial roles of statin and RASI in STEMI [4, 5] are well-known. For these reasons, patients who had not been prescribed these drugs in this study were excluded. The data collection was done via a web-based case report form, at each participating center; well-trained coordinators participated in data collection. The study protocol was approved

by the ethics committee at each participating center and the Chonnam National University Hospital Institutional Review Board (IRB) ethics committee (CNUH-2011-172) according to the ethical guidelines of the 1975 Declaration of Helsinki. All patients provided written informed consent prior to enrollment. All the 17,414 patients completed a 2-year clinical follow-up through face-to-face interviews, phone calls, or chart review.

PCI procedure and medical treatment

Diagnostic coronary angiography and PCI were performed through the femoral and the radial artery approach according to the standard technique [8]. Before PCI, all patients were given loading doses of 200 to 300 mg acetylsalicylic acid (ASA) and 300 to 600 mg clopidogrel, when available; alternatively, 180 mg ticagrelor or 60 mg prasugrel was given. The recommended total duration of dual antiplatelet therapy (DAPT, the combination of ASA [100 mg/day] with clopidogrel [75 mg/day] or ticagrelor [90 mg twice a day] or prasugrel [5–10 mg/ /day]) was more than 12 months to patients who had undergone PCI. Triple antiplatelet therapy (100 mg cilostazol, twice a day added on to DAPT) was left to the discretion of the individual operators. The statins and their doses were as follows: 10–40 mg of atorvastatin, 5–10 mg of rosuvastatin, 2–4 mg of pitavastatin, 10–40 mg of simvastatin, 10–40 mg of pravastatin, 80 mg fluvastatin, and 50–100 mg lovastatin per day. The RASI used and their doses were as follows: 12.5–75 mg of captopril, 2.5–10 mg of ramipril, 2–8 mg of perindopril, 1.25–5 mg of cilazapril, 5–10 mg of imidapril, 7.5–15 mg of moexipril, 2.5–10 mg of enalapril, 5–10 mg of lisinopril, 10 mg of fosinopril, 3.75–7.5 mg of zofenopril, 25–100 mg of losartan, 150–300 mg of irbesartan, 40–160 mg of valsartan, 40–80 mg of telmisartan, 10–20 mg of olmesartan, 4–32 mg of candesartan, 600 mg of eprosartan, and 30–120 mg of fimasartan per day.

Study definitions and clinical outcomes

ST-segment elevation myocardial infarction was defined as the patient who had experienced chest pain with ST-segment elevation ≥ 2 mm in ≥ 2 contiguous precordial lead, or 1 ≥ 1 mm in ≥ 2 limb leads, or new-onset left bundle branch block on the admission electrocardiogram [5]. The major clinical endpoint was the occurrence of MACEs, defined as all-cause death, recurrent myocardial infarction (Re-MI), any repeat coronary revascularization, including target lesion revascularization (TLR), target vessel revascularization (TVR), and non-TVR during the follow-up period. All-cause death was classified as cardiac or non-cardiac. Re-MI was defined as the presence of clinical symptoms, electrocardiographic changes, or abnormal imaging findings of MI, combined with an increase in the creatine kinase myocardial band fraction (CK-MB) above the upper normal limits, or an increase in troponin-T/troponin-I levels above the 99th percentile of the upper normal limit during the follow-up period [5]. TLR was defined as revascularization of the target lesion due to restenosis, or re-occlusion within the stent or 5 mm in and adjacent of the distal or proximal segment. TVR was defined as revascularization of the target vessel or any segment of the coronary artery containing the target lesion. Non-TVR was defined as revascularization of any segment of the non-target coronary artery.

Statistical analysis

All statistical analyses were performed using SPSS software, version 20 (IBM; Armonk, NY, USA). For continuous variables, differences among the three groups were evaluated using the analysis of variance or the Jonckheere-Terpstra test, and post-hoc analysis between two groups was carried out using the Hochberg test or Dunnett-T3 test; data are expressed as the means ± standard deviations. For discrete variables, the differences between two groups among the three groups were analyzed using the χ^2 test or the Fisher exact test, as appropriate; data are expressed as counts and percentages. Only meaningful confounding covariates ($p < 0.001$ or those having predictive values) during the multivariable Cox regression analysis, which are listed were included as follows: age, sex (men), left ventricular ejection fraction (LVEF), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), cardiopulmonary resuscitation (CPR) on admission, primary PCI, hypertension, diabetes mellitus (DM), dyslipidemia, blood N-terminal pro-B-type natriuretic peptide (NT-proBNP), serum creatinine, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), ASA, clopidogrel, ticagrelor, prasugrel, beta-blockers (BBs), calcium channel blockers (CCBs), American College of Cardiology/ /American Heart Association (ACC/AHA) lesion type B2 and C, intravascular ultrasound (IVUS), bare-metal stents (BMS), sirolimus-eluting stent (SES), paclitaxel-eluting stent (PES), everolimus--eluting stents (EES), and biolimus-eluting stents (BES). Various clinical outcomes were estimated using the Kaplan-Meier curve analysis, and dif-

ferences between groups were compared with the log-rank test. A two-tailed p value of < 0.05 indicated statistical significance.

Results

Baseline clinical, laboratory, angiographic, and procedural characteristics

Table 1 shows the baseline, laboratory, angiographic, and procedural characteristics of this cohort study. The study population is composed of patients who had relatively well preserved LVEF (mean 51.2 ± 10.9%). The number of men among the enrolled patients was the highest in group C. The mean ages of the patients enrolled in group A were older than the other groups. The frequency of primary PCI was the highest in group C. In group A, the mean blood levels of CK-MB, troponin-I, NT-proBNP; the prescription rates of more recently developed antiplatelet agents (e.g., ticagrelor, prasugrel) and CCB as the discharge medications; the number of CPR on admission; ACC/AHA type C lesion, the use of IVUS and the deployment of zotarolimus-eluting stent (ZES) were the highest. Moreover, the mean diameter of deployed stents was the lowest in group A. In group B, the number of cardiogenic shocks; the mean value of blood glucose, Hemoglobin A1c, creatinine; the number of clopidogrel as the discharge medication, left anterior descending coronary artery (LAD) as an infarct-related artery, ACC/AHA type B1; and the deployments of BMS, SES, PES, and ≥ 3-vessel disease were the highest. The mean length of the deployed stents was the shortest in group B. In group C, the mean values of BMI, SBP, DBP, total cholesterol, triglyceride, LDL-C; the prescription rate of ASA and BB as the discharge medications; the number of hypertensive patients, LAD as the treated vessel, ACC/AHA type B2 lesion, and EES were the highest. The mean number of deployed stents was not significantly different among the three groups.

Clinical outcomes

Table 2 shows the cumulative incidences of major clinical outcomes during the 2-year follow-up period. After adjustment, the cumulative incidences of MACEs in group A (adjusted hazard ratio [aHR]: 1.337; 95% confidence interval [CI]: 1.064–1.679; p = 0.013) and in group B (aHR: 1.375; 95% CI: 1.149–1.646; p = 0.001) were significantly higher than those in group C (Table 3, Fig. 2A). The cumulative incidence of all-cause death in group A was significantly higher than that in group C (aHR: 1.539; 95% CI: 1.014–2.336; p = 0.043; Fig. 2B). The cumulative incidences of any repeat revascularization (aHR: 1.317; 95% CI: 1.031–1.681; p = 0.028; Fig. 2D), TLR (aHR: 1.754; 95% CI: 0.193–2.580; p = 0.004; Fig. 2E), and TVR (aHR: 1.539; 95% CI: 1.138–2.082; p = 0.005; Fig. 2F) in group B were significantly higher than those in group C. However, the cumulative incidences of cardiac, Re-MI, and non-TVR were similar among the three groups before and after adjustment. Table 4 shows the independent predictors for MACEs at 2 years. LVEF < 50% (aHR: 1.146; 95% CI: 1.019–1.289; p = 0.023), DM (aHR: 1.342; 95% CI: 1.187–1.518; p < 0.001), multivessel disease (aHR: 1.774; 95% CI: 1.570–2.005; p < 0.001), cardiogenic shock (aHR: 0.998; 95% CI: 0.996–1.000; p = 0.043), and CPR on admission (aHR: 2.240; 95% CI: 1.784–2.813; p < 0.001) were significant independent predictors for MACEs.

Discussion

The main findings of this study are as follows: First, the cumulative incidences of MACEs in group A and group B were significantly higher than those in group C. Second, the cumulative incidence of all-cause death in group A was significantly higher than that in group C. Third, the cumulative incidences of any repeat revascularization, TLR, and TVR in group B were significantly higher than those in group C. Finally, the cumulative incidences of cardiac, Re-MI, and non-TVR were similar among the three groups before and after adjustment.

Statins have both fundamental lipid-lowering capacity and additional pleiotropic actions [9]. In patients with STEMI, these pleiotropic activities include cardiovascular death, non-fatal MI, and coronary revascularization rate reduction capabilities [3, 10]. Even though the relative superiority on the long-term clinical outcome between ACEI and ARB in acute MI patients is still debatable [11–13], RASI is recommended in patients with STEMI after PCI [4, 5]. In this study, the cumulative incidence of MACEs, all-cause death, Re-MI, and any repeat revascularization (TLR, TVR, and non-TVR) between group A and group B were similar. It was assumed that the major causative factors for similar results between these two groups are related to a shared process, such as nitric oxide (NO) production [14]. The statins' pleiotropic action include the upregulation and activation of endothelial NO synthase [15], and the accumulated bradykinin after ACEI treatment lead to increased stimulations of the NO production [16]. The combination therapy of statin and RASI compensate unwanted effects

Table 1. Baseline clinical, laboratory, angiographic and procedural characteristics.

Variables	Total (n = 17,414)	Group A Statin alone (n = 2448)	Group B RASI alone (n = 2431)	Group C Statin and RASI (n = 12535)	P			
					Group A vs. B	Group A vs. C	Group B vs. C	Group A vs. B vs. C
Men	13337 (76.6%)	1821 (74.4%)	1842 (75.8%)	9674 (77.2%)	0.264	0.003	0.132	0.007
Age [years]	62.2 ± 12.7	63.1 ± 12.8	62.8 ± 12.9	61.9 ± 12.6	0.439	< 0.001	0.001	< 0.001
LVEF [%]	51.2 ± 10.9	50.5 ± 11.1	51.5 ± 10.8	51.2 ± 10.9	0.381	< 0.001	< 0.001	< 0.001
BMI [kg/m^2]	24.1 ± 3.2	23.8 ± 3.2	23.9 ± 3.3	24.2 ± 3.2	< 0.001	< 0.001	< 0.001	< 0.001
SBP [mmHg]	12.7 ± 27.7	122.7 ± 26.1	125.6 ± 28.5	129.0 ± 27.8	< 0.001	< 0.001	< 0.001	< 0.001
DBP [mmHg]	78.5 ± 16.8	76.0 ± 16.4	77.3 ± 16.9	79.2 ± 16.8	0.009	< 0.001	< 0.001	< 0.001
Cardiogenic shock	972 (5.6%)	162 (6.6%)	163 (6.7%)	647 (5.2%)	0.903	0.004	0.002	0.001
CPR on admission	561 (3.2%)	135 (5.5%)	67 (2.8%)	359 (2.9%)	< 0.001	< 0.001	0.770	< 0.001
Primary PCI	16121 (92.6%)	2256 (92.2%)	2188 (90.0%)	16677 (93.2%)	0.008	0.077	< 0.001	< 0.001
Hypertension	7974 (45.8%)	987 (40.3%)	1129 (46.4%)	5858 (46.7%)	< 0.001	< 0.001	0.792	< 0.001
Diabetes mellitus	4179 (24.0%)	583 (23.8%)	639 (26.3%)	2957 (23.6%)	0.046	0.810	0.004	0.017
Dyslipidemia	1832 (10.5%)	281 (11.5%)	172 (7.1%)	1379 (11.0%)	< 0.001	0.491	< 0.001	< 0.001
Previous MI	472 (2.7%)	79 (3.2%)	60 (2.5%)	333 (2.7%)	0.111	0.114	0.595	0.206
Previous PCI	726 (4.2%)	117 (4.8%)	93 (3.8%)	516 (4.1%)	0.101	0.136	0.506	0.214
Previous CABG	54 (0.3%)	13 (0.5%)	3 (0.1%)	38 (0.3%)	0.013	0.077	0.121	0.036
Previous CVA	887 (5.1%)	113 (4.6%)	130 (5.3%)	644 (5.1%)	0.240	0.281	0.669	0.465
Previous heart failure	121 (0.7%)	21 (0.9%)	30 (1.2%)	70 (0.6%)	0.208	0.081	< 0.001	0.001
Current smokers	8381 (48.1%)	1146 (46.8%)	1160 (47.7%)	6075 (48.5%)	0.527	0.135	0.500	0.297
CK-MB [mg/dL]	175.6 ± 238.9	190.0 ± 2736	184.1 ± 3100	171.2 ± 214.5	0.482	0.001	0.051	0.001
Troponin-I [ng/mL]	64.3 ± 260.2	76.7 ± 619.7	58.3 ± 88.7	63.1 ± 140.3	0.192	0.333	0.046	0.010
Serum glucose [mg/dL]	172.1 ± 74.3	173.1 ± 76.4	176.5 ± 77.1	171.0 ± 73.3	0.128	0.207	0.001	0.013
Hemoglobin A1c (ng/dL)	6.6 ± 2.0	6.6 ± 2.2	6.8 ± 2.9	6.5 ± 1.8	0.178	0.293	0.022	0.020
NT-proBNP [pg/mL]	1515.8 ± 5292.7	2325.2 ± 7028.4	1789.9 ± 4633.6	1324.0 ± 3638.3	0.109	0.002	< 0.001	< 0.001
Hs-CRP [mg/dL]	10.8 ± 60.9	9.8 ± 46.7	11.4 ± 80.4	10.9 ± 58.7	0.467	0.385	0.804	0.523
Serum creatinine [mg/L]	1.06 ± 1.15	1.09 ± 1.54	1.12 ± 1.06	1.05 ± 1.07	0.424	0.281	0.006	< 0.001
Total cholesterol [mg/dL]	185.0 ± 44.2	183.5 ± 44.6	176.8 ± 44.4	186.8 ± 43.8	< 0.001	0.001	< 0.001	< 0.001
Triglyceride [mg/L]	133.8 ± 111.7	128.7 ± 100.9	126.0 ± 102.9	136.3 ± 115.2	0.361	0.001	< 0.001	< 0.001
HDL cholesterol [mg/L]	44.1 ± 18.5	43.5 ± 16.2	44.0 ± 14.0	44.3 ± 19.6	0.242	0.041	0.446	0.008
LDL cholesterol [mg/L]	117.4 ± 40.0	116.0 ± 38.2	110.0 ± 38.9	119.1 ± 40.4	< 0.001	< 0.001	< 0.001	< 0.001

→

Table 1 (cont.). Baseline clinical, laboratory, angiographic and procedural characteristics.

Variables	Total (n = 17,414)	Group A Statin alone (n = 2448)	Group B RASI alone (n = 2431)	Group C Statin and RASI (n = 12535)	P			
					Group A vs. B	Group A vs. C	Group B vs. C	Group A vs. B vs. C
Discharge medications:								
ASA	17278 (99.2%)	2405 (98.2%)	2400 (98.7%)	12437 (99.5%)	0.169	< 0.001	< 0.001	< 0.001
Clopidogrel	15711 (90.2%)	2130 (87.0%)	2346 (96.5%)	11235 (89.6%)	< 0.001	< 0.001	< 0.001	< 0.001
Ticagrelor	931 (5.3%)	170 (6.9%)	26 (1.1%)	735 (5.9%)	< 0.001	0.040	< 0.001	< 0.001
Prasugrel	576 (3.3%)	112 (4.6%)	22 (0.9%)	442 (3.5%)	< 0.001	0.012	< 0.001	< 0.001
Cilostazole	4267 (24.5%)	584 (23.9%)	604 (24.8%)	3079 (24.6%)	0.421	0.457	0.767	0.693
BB	14594 (83.8%)	1657 (67.7%)	2064 (84.9%)	10873 (86.7%)	< 0.001	< 0.001	0.015	< 0.001
CCB	827 (4.7%)	161 (6.6%)	117 (4.8%)	549 (4.4%)	0.008	< 0.001	0.343	< 0.001
Infarct-related artery:								
LM	149 (0.9%)	23 (0.9%)	14 (0.6%)	112 (0.9%)	0.143	0.825	0.117	0.265
LAD	9035 (51.9%)	1207 (49.3%)	1279 (52.6%)	6549 (52.2%)	0.021	0.008	0.741	0.021
LCx	1621 (9.3%)	242 (9.9%)	237 (9.7%)	1142 (9.1%)	0.873	0.226	0.319	0.349
RCA	6598 (37.9%)	976 (39.9%)	898 (36.9%)	4724 (37.7%)	0.035	0.042	0.486	0.073
Treated vessel:								
LM	258 (1.5%)	32 (1.3%)	29 (1.2%)	197 (1.6%)	0.719	0.329	0.161	0.273
LAD	10229 (58.7%)	1371 (56.0%)	1416 (58.2%)	7442 (59.4%)	0.113	0.002	0.303	0.007
LCx	2829 (16.2%)	399 (16.3%)	392 (16.1%)	2038 (16.3%)	0.869	0.960	0.870	0.984
RCA	7417 (42.6%)	1078 (44.0%)	1014 (41.7%)	5325 (42.5%)	0.101	0.155	0.482	0.232
ACC/AHA lesion type:								
Type B1	2508 (14.4%)	358 (14.6%)	405 (16.7%)	1745 (13.9%)	0.050	0.360	< 0.001	0.002
Type B2	5060 (29.1%)	615 (25.1%)	684 (28.1%)	3761 (30.0%)	0.017	< 0.001	0.065	< 0.001
Type C	8193 (47.0%)	1232 (50.3%)	1032 (42.5%)	5929 (47.3%)	< 0.001	0.006	< 0.001	< 0.001
Extent of CAD:								
1-vessel	9078 (52.1%)	1287 (52.6%)	1220 (50.2%)	6571 (52.4%)	0.095	0.890	0.043	0.116
2-vessel	5201(29.9%)	753 (30.8%)	737 (30.3%)	3711 (29.6%)	0.737	0.253	0.482	0.455
≥ 3-vessel	3135 (18.0%)	408 (16.7%)	474 (19.5%)	2253 (18.0%)	0.010	0.122	0.075	0.036
IVUS	2397 (13.8%)	371 (15.2%)	278 (11.4%)	1748 (13.9%)	< 0.001	0.116	0.001	< 0.001
OCT	29 (0.2%)	2 (0.1%)	2 (0.1%)	25 (0.2%)	0.994	0.298	0.213	0.233
FFR	104 (0.6%)	16 (0.7%)	2 (0.1%)	86 (0.7%)	0.001	0.858	< 0.001	0.002

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Table 1 (cont.). Baseline clinical, laboratory, angiographic and procedural characteristics.

Variables	Total (n = 17,414)	Group A Statin alone (n = 2448)	Group B RASI alone (n = 2431)	Group C Statin and RASI (n = 12535)	P			
					Group A vs. B	Group A vs. C	Group B vs. C	Group A vs. B vs. C
Types of stent:								
BMS	1127 (6.5%)	105 (4.3%)	185 (7.6%)	837 (6.7%)	< 0.001	< 0.001	0.095	< 0.001
SES	2865 (16.5%)	376 (15.4%)	558 (23.0%)	1931 (15.4%)	< 0.001	0.955	< 0.001	< 0.001
PES	2446 (14.0%)	313 (12.8%)	466 (19.2%)	1667 (13.3%)	< 0.001	0.493	< 0.001	< 0.001
ZES	3869 (22.2%)	585 (23.9%)	486 (20.0%)	2798 (22.3%)	0.001	0.088	0.011	0.004
EES	4754 (27.3%)	693 (28.3%)	480 (19.7%)	3581 (28.6%)	< 0.001	0.795	< 0.001	< 0.001
BES	1343 (7.7%)	203 (8.3%)	100 (4.1%)	1040 (8.3%)	< 0.001	0.994	< 0.001	< 0.001
Stent diameter [mm]	3.20 ± 0.42	3.18 ± 0.44	3.20 ± 0.42	3.20 ± 0.42	0.044	0.008	0.956	0.007
Stent length [mm]	25.9 ± 9.0	26.1 ± 9.4	24.8 ± 7.0	26.1 ± 9.2	< 0.001	0.973	< 0.001	0.011
Number of stent	1.40 ± 0.72	1.40 ± 0.71	1.38 ± 0.70	1.41 ± 0.73	0.511	0.430	0.100	0.222

Values are means ± standard deviation or numbers and percentages. The p value for continuous data was obtained from the analysis of variance or the Jonckheere-Terpstra test. The p value for categorical data was obtained from the chi-square or the Fisher's exact test. Group A — statin alone; Group B — RASI alone; Group C — both statin and RASI; LVEF — left ventricular ejection fraction; BMI — body mass index; SBP — systolic blood pressure; DBP — diastolic blood pressure; CPR — cardiopulmonary resuscitation; PCI — percutaneous coronary intervention; MI — myocardial infarction; CABG — coronary artery bypass grafting; CVA — cerebrovascular accidents; CK-MB — creatinine kinase myocardial band; NT-proBNP — N-terminal pro-B-type natriuretic peptide; Hs-CRP — high sensitivity C-reactive protein; HDL — high-density lipoprotein; LDL — low-density lipoprotein; ASA — acetylsalicylic acid; BB — beta-blockers; CCB — calcium channel blockers; LM — left main coronary artery; LAD — left anterior descending coronary artery; LCx — left circumflex coronary artery; RCA — right coronary artery; ACC/AHA — American College of Cardiology/American Heart Association; CAD — coronary artery disease; IVUS — intravascular ultrasound; OCT — optical coherence tomography; FFR — fractional flow reserve; BMS — bare-metal stents; SES — sirolimus-eluting stents; PES — paclitaxel-eluting stents; ZES — zotarolimus-eluting stents; EES — everolimus-eluting stents; BES — biolimus-eluting stents

Table 2. Cumulative clinical events at 2 years.

Variables	Total (n = 17,414)	Group A (n = 2448)	Group B (n = 2431)	Group C (n = 12,535)	P			
					Group A vs. B	Group A vs. C	Group B vs. C	Group A vs. B vs. C
MACEs	1262 (7.2%)	193 (7.9%)	214 (8.8%)	855 (6.8%)	0.246	0.059	0.001	0.001
All-cause death:	358 (2.1%)	67 (2.7%)	59 (2.4%)	232 (1.9%)	0.528	0.004	0.060	0.007
Cardiac death	248 (1.4%)	44 (1.8%)	39 (1.6%)	165 (1.3%)	0.602	0.063	0.262	0.133
Re-MI:	257 (1.5%)	44 (1.8%)	32 (1.3%)	181 (1.4%)	0.175	0.188	0.627	0.324
Any repeat revascularization:	737 (4.2%)	94 (3.8%)	136 (5.6%)	507 (4.0%)	0.004	0.637	0.001	0.001
TLR	246 (1.4%)	34 (1.4%)	52 (2.1%)	160 (1.3%)	0.046	0.653	0.001	0.004
TVR	426 (2.4%)	50 (2.0%)	82 (3.4%)	294 (2.3%)	0.004	0.360	0.003	0.004
Non-TVR	323 (1.9%)	44 (1.8%)	57 (2.3%)	222 (1.8%)	0.179	0.928	0.056	0.155

Values are means ± standard deviation or numbers and percentages. The p values for categorical data were obtained from chi-square or Fisher's exact test. Group A — statin alone; Group B — RASI alone; Group C — both statin and RASI; MACEs — major adverse cardiac events; Re-MI — recurrent myocardial infarction; TLR — target lesion revascularization; TVR — target vessel revascularization

Table 3. Hazard ratio for 2-year major clinical outcomes by Cox-proportional hazard ratio analysis.

	Hazard ratio (95% confidence interval), P		
	Group A vs. B	Group A vs. C	Group B vs. C
MACE:			
Unadjusted	1.057 (0.870–1.285), 0.574	1.187 (1.016–1.388), 0.031	1.256 (1.081–1.459), 0.003
Adjusted*	1.093 (0.822–1.454), 0.540	1.337 (1.064–1.679), 0.013	1.375 (1.149–1.646), 0.001
All-cause death:			
Unadjusted	1.185 (0.835–1.681), 0.343	1.506 (1.148–1.977), 0.003	1.275 (0.958–1.696), 0.096
Adjusted*	1.386 (0.803–2.390), 0.241	1.539 (1.014–2.336), 0.043	1.172 (0.767–1.793), 0.463
Cardiac death:			
Unadjusted	1.164 (0.756–1.792), 0.490	1.386 (0.994–1.933), 0.054	1.192 (0.841–1.690), 0.323
Adjusted*	1.125 (0.528–2.394), 0.768	1.090 (0.609–1.951), 0.772	1.244 (0.726–2.131), 0.426
Re-MI:			
Unadjusted	1.434 (0.910–2.262), 0.121	1.276 (0.918–1.774), 0.147	1.135 (0.779–1.652), 0.510
Adjusted	1.048 (0.528–2.081), 0.894	1.041 (0.637–1.699), 0.873	1.180 (0.725–1.921), 0.499
Any repeat revascularization:			
Unadjusted	1.377 (1.059–1.791), 0.017	1.024 (0.822–1.276), 0.831	1.345 (1.113–1.625), 0.002
Adjusted*	1.038 (0.712–1.513), 0.847	1.263 (0.926–1.722), 0.141	1.317 (1.031–1.681), 0.028
TLR:			
Unadjusted	1.450 (0.941–2.234), 0.092	1.119 (0.773–1.620), 0.119	1.624 (0.188–2.221), 0.002
Adjusted*	1.111 (0.618–1.998), 0.724	1.648 (0.999–2.717), 0.050	1.754 (0.193–2.580), 0.004
TVR:			
Unadjusted	1.555 (1.094–2.210), 0.014	1.116 (0.827–1.506), 0.474	1.391 (1.089–1.777), 0.008
Adjusted*	1.184 (0.736–1.905), 0.487	1.286 (0.857–1.930), 0.224	1.539 (1.138–2.082), 0.005
Non-TVR:			
Unadjusted	1.230 (0.830–1.823), 0.302	1.004 (0.755–1.442), 0.796	1.284 (0.960–1.718), 0.092
Adjusted*	1.067 (0.578–1.968), 0.836	1.166 (0.721–1.886), 0.531	1.074 (0.717–1.610), 0.729

*Adjusted model was included age, gender (men), LVEF, BMI, SBP, DBP, CPR on admission, primary PCI, hypertension, DM, dyslipidemia, N-proBNP, serum creatinine, total cholesterol, triglyceride, LDL-cholesterol, ASA, clopidogrel, ticagrelor, prasugrel, BB, CCB, ACC/AHA lesion type B2 and C, IVUS, BMS, SES, PES, EES, BES. Abbreviations — see Table 1

of statin and has additive or synergistic effects on endothelial dysfunction, inflammation, and lipid profiles [17–19]. Furthermore, the statin plus RASI combination reduced cardiovascular events more than statin alone and to a greater extent than RASI therapy alone [18, 20]. As expected, additional beneficial effects of the statin and RASI combination therapy were observed in reducing MACEs compared to that achieved with monotherapy alone in this study. Previous studies have shown that both the statin and the RASI could reduce the death rate and revascularization rate in STEMI patients [21–23]. Additionally, the relative superiority between these two abilities, according to the drugs, was suspected in this study. Figure 2B shows the Kaplan-Meier curve of all-cause death among the three groups. The cumulative incidence of all-cause death in group A was continuously higher than that in group C during the 2-year follow-up period. However, the cumulative incidence of all-cause death between group B and group C was statistically insignificant. In contrast, the cumulative incidence of total revascularization in group B was continuously higher than that in group C (Fig. 2D). The cumulative incidence between group A and group C was insignificantly different. The Kaplan-Meier curve of TLR (Fig. 2E) and TVR (Fig. 2F) also showed similar patterns among the three groups. Regarding the results of this study, it was cautiously supposed that the possibility that RASI was more likely related with mortality reduction rather than revascularization reduction, and statin was more likely related with repeat revascularization reduction rather than mortality reduction in these STEMI patients after successful stent implantation. In this study, independent predictors for MACEs at 2 years were decreased LVEF (< 50%), DM, multivessel disease, cardiogenic shock, and CPR on admission (Table 4). Therefore, in these situations, the combination therapy of statin and RASI might be helpful in reducing MACEs.

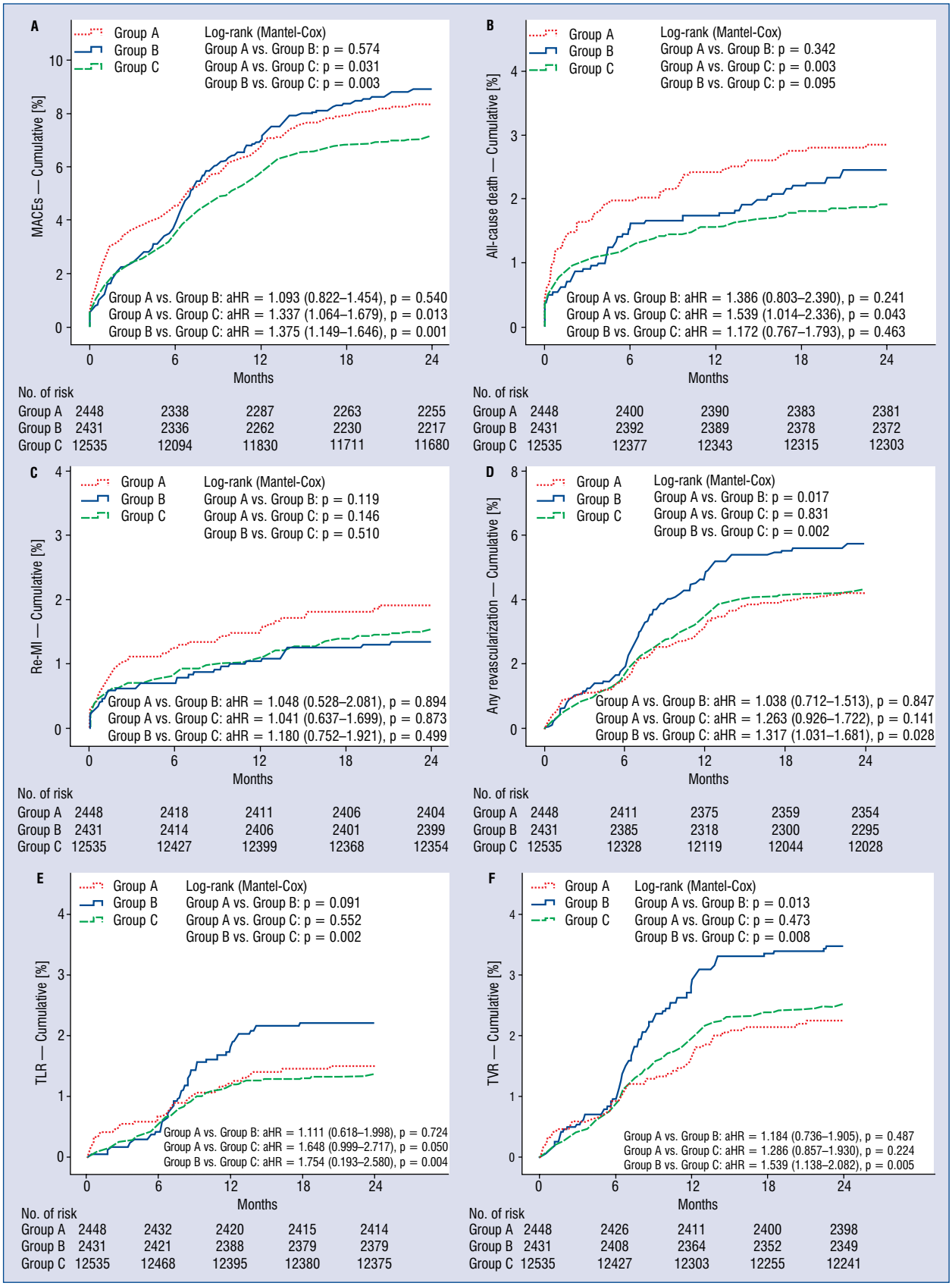

Figure 2. Kaplan-Meier curved analysis for major adverse cardiac events (MACEs; **A**), all-cause death (**B**), recurrent myocardial infarction (Re-MI; **C**), any repeat revascularization (**D**), target lesion revascularization (TLR; **E**), and target vessel revascularization (TVR; **F**) during a 2-year follow-up perioad d; aHR — adjusted hazard ratio.

Table 4. Multivariate Cox-proportional regression analysis for independent predictor of MACEs.

Variables	Unadjusted		Adjusted	
	HR (95% CI)	P	HR (95% CI)	P
Groups				
A vs. B	1.057 (0.870–1.285)	0.574	1.063 (0.870–1.298)	0.550
A vs. C	1.187 (1.016–1.388)	0.031	1.208 (1.037–1.408)	0.019
B vs. C	1.256 (1.081–1.459)	0.003	1.217 (1.044–1.418)	0.012
Age, ≥ 65 years	1.042 (1.013–1.071)	0.004	1.034 (0.990–1.081)	0.129
Gender, men	1.208 (1.066–1.367)	0.003	1.038 (0.899–1.199)	0.281
LVEF, < 50%	1.248 (1.118–1.394)	< 0.001	1.146 (1.019–1.289)	0.023
Hypertension	1.211 (1.084–1.352)	0.001	1.082 (0.961–1.217)	0.192
Diabetes mellitus	1.481 (1.315–1.667)	< 0.001	1.342 (1.187–1.518)	< 0.001
Dyslipidemia	1.066 (0.894–1.271)	0.478	1.027 (0.857–1.232)	0.772
Previous MI	1.373 (1.020–1.849)	0.037	1.206 (0.890–1.633)	0.227
Multi-vessel disease	1.897 (1.691–2.129)	< 0.001	1.774 (1.570–2.005)	< 0.001
Current smokers	1.145 (1.025–1.279)	0.017	1.043 (0.869–1.251)	0.842
Cardiogenic shock	1.301 (1.049–1.614)	0.017	1.135 (0.908–1.419)	0.043
CPR on admission	2.385 (1.941–2.972)	< 0.001	2.240 (1.784–2.813)	< 0.001
ACC/AHA type B2/C	1.027 (0.902–1.168)	0.689	1.028 (0.900–1.174)	0.701
Stent diameter, < 3.0 mm	1.242 (1.093–1.412)	0.001	1.116 (0.978–1.273)	0.103
Stent length, ≥ 28 mm	1.149 (1.027–1.285)	0.015	1.048 (0.934–1.176)	0.421
LAD — IRA	1.002 (0.898–1.119)	0.967	1.072 (0.881–1.305)	0.541
LAD — treated vessel	1.158 (1.034–1.298)	0.011	1.190 (0.978–1.447)	0.083
IVUS	1.117 (0.956–1.307)	0.164	1.083 (0.923–1.271)	0.329

HR — hazard ratio; CI — confidence interval; IRA — infarct-related artery; other abbreviations — see Table 1

Unlike previous studies [18, 24], the present study population was composed of solely STEMI patients. While some previous studies [25, 26] were conducted before the widespread use of statin and dual antiplatelet agents, diverse kinds of statins and newly developed antiplatelet agents were used in this study. More than 50 high-volume University or community hospitals with facilities for primary PCI and onsite cardiac surgery in South Korea participated in this study. Therefore, this comparative study might provide meaningful information to interventional cardiologists regarding the importance of a statin and RASI combination therapy rather than a monotherapy of each drug, and some different clinical outcome characteristics of the statin monotherapy and RASI monotherapy compared with a combination therapy in STEMI patients, after successful stent implantation during a 2-year follow-up period.

Limitations of the study

This study had several limitations. First, there may be some under-reporting and/or missed data due to limitations of registry data. Second, this study was based on medications at discharge, and this registry data did not include a full detailed data concerning the starting times of statin and RASI therapy, change of prescription doses, long-term adherence, and discontinuation during the follow-up period; these factors might, therefore, act as substantial bias in this study. Third, the achievement of target blood cholesterol level (i.e., LDL-C) was a critical prognostic parameter after statin therapy during the follow-up period. However, the follow-up results could not presented for these lipid profiles due to a limitation of the registry data, which might act as a bias. Fourth, because this study reflectsa multicenter "real-world" clinical practice, diverse kinds and doses of statins and RASI were prescribed; all of which could not be adjusted during statistical analysis, and might be another limitation of this study. Fifth, the selection of either monotherapy or combination therapy of statin and RASI after PCI was left to physician preferences; which might act as selection bias. Sixth, a multivariate analysis was done to strengthen the present results; variables

not included in this registry may have affected the study outcomes.

Conclusions

In conclusion, a statin and RASI combination therapy significantly reduced the cumulative incidence of MACEs compared with a monotherapy of these drugs. Moreover, this combination therapy showed a reduced all-cause death rate compared with statin monotherapy, and a decreased repeat revascularization rate compared with RASI monotherapy.

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Isoprenaline induced Takotsubo syndrome: Histopathological analyses of female rat hearts

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Abstract

Background: *Takotsubo syndrome (TTS) is a stress-induced disorder affecting mostly postmenopausal women. The aim of the study was to evaluate isoprenaline (ISO) dependent female rat model and histopathological characteristics in TTS.*

Methods: *Forty-nine Sprague Dawley female rats, 12 weeks old, were injected intraperitoneally with a single dose of ISO at doses 50 (n = 8), 75 (n = 6), 100 (n = 3), 150 (n = 27) and 200 (n = 5) mg/kg body weight (bw). The control group (n = 6) was injected with physiological saline. The echocardiographic examination to assess wall motion abnormalities took place 24, 48, 72 h, and 7 days post-ISO. Histopathological analysis was performed on the basis of hematoxylin-eosin staining.*

Results: *The total mortality rate was 3/49 (6.12%). The optimum dose of ISO to induce TTS was 150 mg/kg bw and 21/27 (77.77%) rats showed apical ballooning. Histopathological analysis revealed focal necrosis/apoptosis of cardiomyocytes with inflammatory and fibroblast-like cell infiltration. Foci were the most numerous in the central muscle layer with apical-basal gradient 24, 48, 72 h post-ISO ($p < 0.05$). Significant differences were noted 48 h post-ISO in the central layer in apical vs basal segments ($p = 0.0032$), in the endocardial layer in apical vs basal segments (0.00024) and in mid-cavital vs. basal segments ($p = 0.0483$). The number of foci in endocardium of apical region differ 48 h post-ISO in rats with a dose of 150 vs. 200 mg/kg bw ($p = 0.0084$).*

Conclusions: *The ISO female rat model of TTS is associated with higher optimum dose and lower mortality in comparison with the male TTS model. TTS presents as a singles cardiomyocyte disorder, foci concerned mainly central muscle layer with apical-basal gradient.* (Cardiol J 2022; 29, 1: 105–114)

Key words: Takotsubo syndrome, female rat model, stress-induced cardiomyopathy, reversible heart failure

Introduction

Acute reversible heart failure induced by both emotional and physical stressors characterize Takotsubo syndrome (TTS). Clinical presentation of this pathology is similar to acute myocardial infarction with an echocardiographic view of the left ventricle (LV) with akinetic apical segments and a ventriculogram that resembles the Japanese pot (called takotsubo) used to capture octopuses. Most interesting is the fact that the syndrome concerns women in about 90% of the cases [1–4]. The disease

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may relapse even after 10 years after the first episode and may reappear anytime in the future [5, 6]. Mostly, it is observed in individuals between 65 and 70 years old but has even been documented in a 90-year-old woman [7]. The pathophysiology of the disease is unknown. In the literature, several hypotheses have been proposed. TTS may result from multivessel epicardial coronary spasm, or may be associated with coronary microvasculature impairment, or may reflect activation of central neurogenic mechanisms analogous to those evoked by subarachnoid hemorrhage, or finally it can be related to catecholamine cardiotoxicity [8–10]. The last hypothesis presents as the most interesting, because in these patients elevated plasma catecholamine concentrations were observed. Lyon et al. [8] have suggested that the high circulating epinephrine serum level might trigger a switch in cardiomyocyte intracellular signaling after occupation of β2-adrenoceptors from Gs protein to Gi protein that produces a negative inotropic effect. The switch may have a protective role since high levels of β1-adrenoceptors Gs protein pathway activation induce apoptotic pathways in the cardiomyocytes [2, 8]. Mori et al. [11] presented that the canine heart has a higher concentration of β-adrenoreceptors in the apical myocardium with the concentration gradient decreases from the apex to the base and that may explain apical ballooning typical for TTS. Heart histopathology in TTS has not been studied enough. Human myocardial biopsies revealed interstitial infiltrates consisting of mononuclear lymphocytes, leukocytes, macrophages, and additionally myocardial fibrosis, necrosis and apoptosis [1, 12].

Shao et al. [13] presented a male rat model of TTS related to isoprenaline (ISO) intraperitoneal administration that enables a better understanding of the disease [13]. ISO is a synthetic β-sympathomimetic amine that is structurally related to epinephrine, which increases myocardial oxygen requirements [14]. TTS may be induced by ISO at doses ≥ 50 mg/kg body weight (bw) in male rats. Regional akinesia in this model was completely resolved within 7 days. Histopathological analysis revealed lipid accumulation and fibrosis in the region of stunned myocardium [13]. Therefore, the aim of the present study was to characterize the histopathology of ISO induced TTS in female rats since the disease mainly concerns women.

Methods

The experimental procedures were designed in accordance with and approved by The Local Animal Research Ethics Committee of the Medical University of Warsaw. In this study, 55 Sprague Dawley female rats were used with a mean bw of 210 g. The rats were housed in a temperature-controlled facility (22–25°C), humidity 60% with a 12 h light/dark cycle and given free access to food and water. A single dose of ISO was intraperitoneally (IP) injected to induce TTS in 49 female rats. Doses of ISO: 50, 75, 100, 150, 200 mg/kg bw were tested to identify the optimum dose and minimum dose necessary to induce LV akinesia in female rats. The control group consisted of 6 female rats that were IP injected with physiological saline (NaCl).

Transthoracic echocardiography

Baseline echocardiograms were performed for all rats under general anesthesia (ketamine 10 mg/100 g bw with xylazine 1 mg/100 g bw, IP). Two-dimensional images were recorded in short and long axis views. Baseline echocardiographic values were recorded to identify LV akinesia typical for TTS [13, 15, 16]. The transthoracic echocardiography was performed, and the results were analyzed in a blinded manner.

In the control group, echocardiography was performed 24 h post-NaCl. In the experimental group with a dose of 150 mg/kg bw, echocardiography was performed 24 h post-ISO and additionally after 48 h (n = 6), 72 h (n = 7), 7 days (n = 7). In the group with a dose of 200 mg/kg bw, echocardiography was performed 24 h and 48 h post-ISO. In the low dose groups: 50–100 mg/kg bw, echocardiography was performed 6 h and 24 h post-ISO.

Takotsubo cardiomyopathy induction

In 8 rats — an ISO dose of 50 mg/kg bw was administered, in 6 rats — 75 mg/kg bw, in 3 rats — 100 mg/kg bw, in 27 rats – 150 mg/kg bw, in 5 rats — 200 mg/kg bw. In the group with a dose of 150 mg/kg bw, 1/27 died and 6/27 rats were sacrificed 24 h post-ISO, 6/27 after 48 h, 7/27 after 72 h, and 7/27 after 7 days (Fig. 1); in the group with a dose of 200 mg/kg bw, 5 rats were sacrificed 48 h post-ISO; and in the control group, 6 rats were sacrificed 24 h post-NaCl.

Histopathological analysis

The hearts of the sacrificed animals treated with doses of 150 and 200 mg/kg bw and from the control group were fixed in 4% formaldehyde and cut into four fragments: apical, basal, and mid-cavity segments. Additionally, the mid-cavity segments were cut horizontally to identify their central parts. Heart fragments were embedded

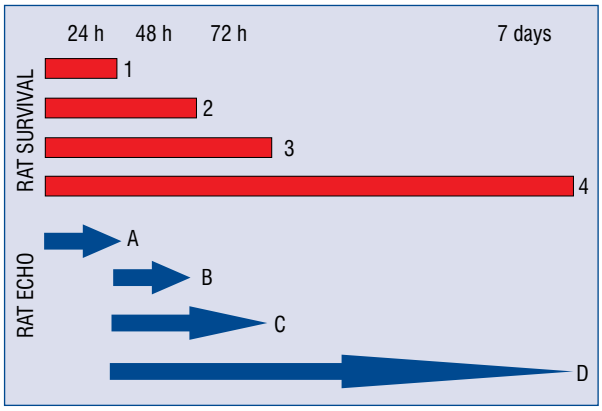

Figure 1. Summary of echocardiography analysis and rat survival in the subgroup treated with the dose 150 mg/kg body weight 24 hours post isoprenaline (ISO) administration all (27) animals underwent echo analysis (A) and 1 rat died and 6/27 were sacrificed (1). 48 hours post ISO 6/27 rats underwent echo (B) and were sacrificed (2). 72 hours post ISO 7/27 rats underwent echo (C) and were sacrificed (3). 7 days post ISO 7/27 rats underwent echo (D) and were sacrificed (4).

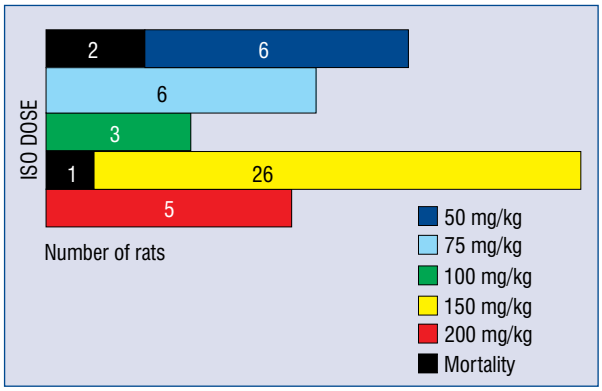

Figure 2. Summary of rat survival and mortality; ISO — isoprenaline.

in paraffin and cut into 4 μm sections. Finally, hematoxylin and eosin and Trichrom blue staining were performed. The morphological and quantitative studies were performed. Apical, mid-cavity, and basal segments of the right ventricle (RV) and LV were analyzed. Additionally, in all three segments of LV, the epicardial, central, and endocardial muscle layers were evaluated. Inflammatory cells (macrophages, lymphocytes, neutrophils) mobilization and their focal accumulation, mitosis of infiltrating cells, cardiomyocyte vacuolization, cardiomyocyte necrosis/apoptosis, interstitial edema (IE), cardiomyocyte hypertrophy, foam cells, fibroblast-like cells and collagen accumulation were taken into consideration.

Statistical analysis

The Shapiro-Wilk and Levene tests were used. The Kruskal-Wallis test was performed to identify significant differences between the means of the analyzed values (mean number, ± standard deviation) and was followed by multiple comparison post-hoc tests. Data was analyzed in the Statistica 10 application. $P < 0.05$ was considered statistically significant.

Results

Takotsubo syndrome induction by ISO administration in female rats

Low doses of ISO were associated with a rare presence of motion abnormalities in echocardiography. Only 1/8 (12.5%) in the group with an ISO dose of 50 mg/kg bw, 2/6 (33.3%) in the 75 mg/kg bw group, and 0/3 (0%) in the 100 mg/kg bw group possessed features of TTS in echocardiography. An ISO dose of 150 mg/kg bw appeared to be the optimum dose since 21/27 (77.77%) of the rats presented apical akinesia in echocardiographic examination 24 h post-ISO. A dose of 200 mg/kg bw was also administered, however, none of the 5 examined rats presented echocardiographic features of TTS. The total mortality rate in the experimental group was 3/49 (6.12%) and was observed in the first 24 h post-ISO (2 in the group with an ISO dose of 50 mg/kg [2/8; 25%] without akinesia typical for TTS, with significant bradycardia; and 1 in the group with an ISO dose of 150 mg/kg [1/27; 3.7%] with severe bradycardia and extensive LV akinesia) (Figs 1, 2).

Histopathological analysis

In the control group, 24 h post-NaCl, normal cardiomyocytes and vasculature of the heart were observed (Fig. 3A, B).

Histopathology: Morphological analysis in the hearts of rats with TTS (post-ISO 150 mg/kg bw)

In the group sacrificed **24 h post-ISO**, focal cardiomyocyte necrosis/apoptosis and vacuolization of neighboring cardiomyocytes were observed in apical, mid-cavital and basal segments of LV and in RV (Fig. 3C, D). Foci were not observed in the epicardium of LV (Fig. 3), while in RV they were located in all heart muscle layers (Fig. 4). Foci of cardiomyocyte necrosis/apoptosis contained macrophages, fibroblast-like cells and rarely neutrophils. Foci of cardiomyocyte necrosis/apoptosis with inflammatory cells infiltration were much bigger in RV than in LV. Inflammatory cells mobili-

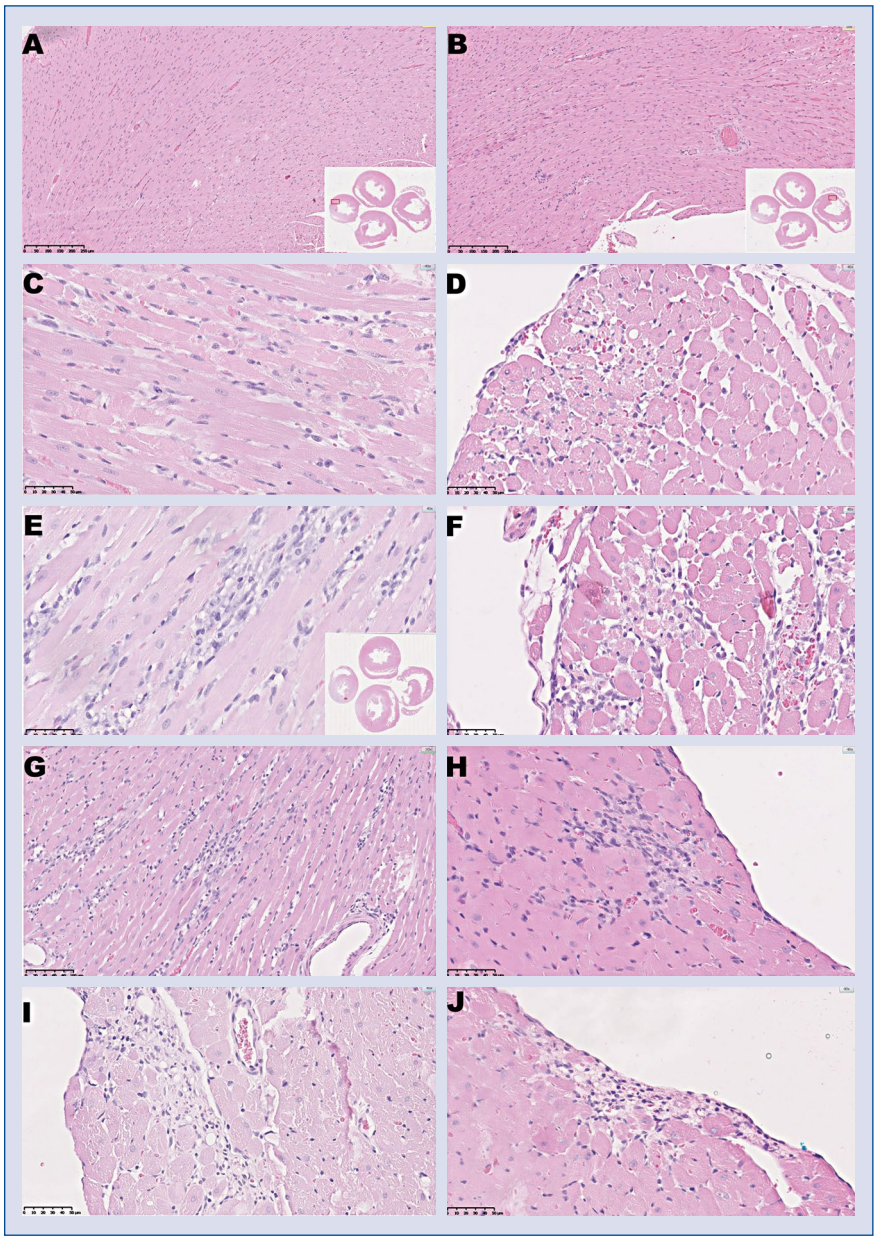

Figure 3. Histopathological abnormalities in the hearts of rats with Takotsubo syndrome (TTS) treated with isoprenaline (ISO) dose 150 mg/kg body weight in comparison to control rats treated with NaCl; **A.** Apical segments of myocardium. Normal cardiac muscle and vessels; **B.** Basal segments of myocardium. Normal cardiac muscle and vessels; **C.** Apical segment of myocardium 24 h after ISO administration. Focal necrosis/apoptosis of single cardiomyocytes (less than 5 per foci). Few macrophages and rare neutrophils. Mitosis of infiltrating cells. Features of inflammatory and fibroblast-like cells mobilization; **D.** Midventricular segments of myocardium 24 h after ISO administration. Focal single cardiomyocyte necrosis/apoptosis with macrophages, neutrophils infiltration. Vacuolization of cardiomyocytes with few large vacuoles. Interstitial edema with cardiomyocytes drawn aside; **E.** Apical segments of myocardium 48 h after ISO administration. Large foci of chronic inflammation, without cardiomyocyte necrosis/apoptosis. Mitosis of infiltrating cells. Less expressed interstitial edema; **F.** Middle segments of myocardium 48 h after ISO administration. Focal mononuclear cell infiltration. Interstitial edema. Small hemorrhages. Irregular shape, enlarged cardiomyocytes. Collagen deposits; **G.** Apical segments of myocardium 72 h after ISO administration. Large foci of granulation tissue. Mitosis of infiltrating cells. Collagen deposits; **H.** Middle segments of myocardium 72 h after ISO administration. Large foci of granulation tissue, chronic inflammation, collagen deposits. Enlarged cardiomyocytes with blur contours and structure; **I.** Apical segments of myocardium 7 days post ISO administration. Smaller foci of inflammation with fibroblasts and focal fibrosis. The features of cardiac hypertrophy are also visible; **J.** Middle segments of myocardium 7 days post ISO administration. Smaller subendocardial foci of inflammation with fibroblasts and focal fibrosis. The features of cardiac hypertrophy are also visible.

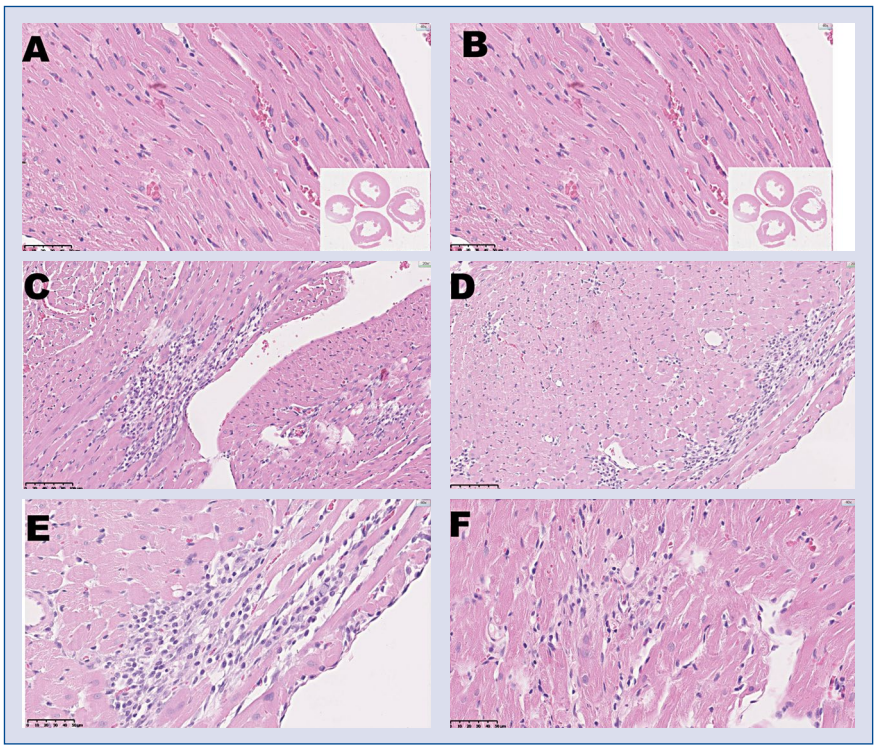

Figure 4. Takotsubo syndrome-histopathological abnormalities in right ventricle (RV); **A, B.** Control rat hearts. Mid--cavity segments of RV. Normal cardiac muscle and vasculature; **C.** 24 h after isoprenaline (ISO) administration. Larger focal cardiomyocyte necrosis/apoptosis with more inflammatory and fibroblast-like cell infiltrations than observed in left ventricle. Cardiomyocyte vacuolization. Slight edema mainly around vessels; **D.** 48 h after ISO administration. Foci of mononuclear inflammatory cell infiltration. Mitosis of infiltrating cells; **E.** 72 h after ISO administration. Foci of granulation tissue. Collagen deposits; **F.** Seven days after ISO administration. Single smaller foci of inflammatory cell infiltration. Foci of collagen deposits. Features of cardiomyocyte hypertrophy and lipid accumulation. Disrupted architecture of singles cardiomyocytes.

zation were accompanied by features of vascularization. Mitosis of infiltrating cells was observed. IE was visible (Fig. 3C, D).

48 h post-ISO larger foci of inflammatory and fibroblast-like cells infiltration with a mononuclear inflammation pattern without cardiomyocyte necrosis/apoptosis were observed. Mitosis of infiltrating cells were seen. Vacuolization of cardiomyocytes was not distinguishable in most rats. IE was less expressed. Foam cells rarely appeared. Additionally, small focal hemorrhages were noticed (Fig. 3E, F).

72 h post-ISO foci of granulation tissue were observed, fibroblast-like cells, without damaged cardiomyocytes, without cardiomyocyte vacuolization, without IE but with collagen deposits. Cardiomyocytes neighboring foci were larger with blur contours and structures that may suggest cardiomyocyte edema. Mitosis of infiltrating cells was visible (Fig. 3G, H).

7 days post-ISO 4/7 rats presented normal echocardiographic function of the heart and histopathology revealed almost normal cardiac structure. Small collagen deposits were seen with focal foam cells, single, small, residual foci of inflammation. In 3/7 rats, heart motion abnormalities persisted and histopathological analysis showed rare foci of mononuclear cells, scattered collagen deposits and foam cells. In all hearts diagnosed with TTS, cardiomyocytes focally presented features of hypertrophy (Fig. 3I, J).

Histopathology: Quantitative analysis in the hearts of rats with TTS (post-ISO 150 mg/kg bw)

24 h post-ISO the number of foci in the endocardial muscle layer was from 0 to 12 in the field of view (i.f.v. 200×), 0 to 13 i.f.v. in the central cardiac muscle layer, and 0 to 6 i.f.v. in RV of apical segments. The foci were more numerous in the apical than in basal segments of LV in central muscle layer

Table 1. The mean number of foci of inflammatory cells, fibroblast-like cells arranged originally in neighborhood of apoptotic/necrotic cardiomyocytes in rats with Takostubo syndrome (TTS).

Localization	24 h post-ISO (min–max)	48 h post-ISO (min–max)	72 h post-ISO (min–max)	7 days post-ISO (min–max)	P	7 days post-ISO without TTS
Apical segments; epicardial layer	0	0.2 ± 0.4 (0–1)	0.3 ± 0.5 (0–1)	0	> 0.05	0
Apical segments; central layer	6.8 ± 4.2 (0–13)	7.7 ± 4.5 (3–13)	8.5 ± 3.8 (4–13)	3.3 ± 2.7 (0–8)	> 0.05	2.7 ± 2.1 (1–5)
Apical segments; endocardial layer	6.0 ± 4.3 (0–12)	5.8 ± 1.7 (4–8)	3.5 ± 2.1 (0–5)	2.7 ± 1.5 (0–4)	> 0.05	3.7 ± 0.6 (3–4)
Apical segments; right ventricle	3.3 ± 2.3 (0–6)	3.0 ± 1.5 (1–5)	2.8 ± 2.3 (0–7)	1.6 ± 1.7 (0–5)	> 0.05	1.3 ± 0.6 (1–2)
Mid-cavity segments; epicardial layer	0	0	0	0		0
Mid-cavity segments; central layer	3.0 ± 2.7 (0–8)	3.8 ± 2.0 (1–7)	6.3 ± 4.5 (2–14)	1.7 ± 1.3 (0–2)	> 0.05	1.7 ± 0.6 (1–2)
Mid-cavity segments; endocardial layer	4.2 ± 4.4 (0–12)	4.3 ± 2.3 (2–8)	6.7 ± 4.5 (2–11)	2.1 ± 2.3 (0–6)	> 0.05	1.3 ± 1.5 (0–3)
Mid-cavity segments; right ventricle	3.3 ± 2.8 (0–8)	2.2 ± 1.5 (0–4)	2.7 ± 2.3 (1–6)	1.9 ± 1.3 (0–4)	> 0.05	2.0 ± 2.0 (0–4)
Basal segments; epicardial layer	0	0	0	0		0
Basal segments; central layer	1.2 ± 1.0 (0–2)	0.8 ± 1.0 (0–2)	2.5 ± 1.6 (0–4)	0.9 ± 1.2 (0–3)	> 0.05	1.3 ± 1.5 (0–3)
Basal segments; endocardial layer	1.3 ± 1.8 (0–4)	0.3 ± 0.8 (0–2)	3.0 ± 4.6 (0–11)	1.1 ± 1.9 (0–5)	> 0.05	2.3 ± 2.5 (0–5)
Basal segments; right ventricle	2.5 ± 2.1 (0–6)	3.2 ± 1.6 (1–5)	2.8 ± 2.3 (0–6)	1.9 ± 2.0 (0–4)	> 0.05	1.7 ± 2.1 (0–4)

ISO — isoprenaline

6.8 ± 4.2 vs. 1.2 ± 1.0 ($p = 0.0449$). The muscle of RV was equally affected (3.3 ± 2.3 vs. 3.3 ± 2.8 vs. 2.5 ± 2.1 i.f.v. of apical, mid-cavital, and basal segments respectively; $p > 0.05$). Foci of inflammatory cell infiltrations around cardiomyocytes with features of cardiomyocyte necrosis/apoptosis were also frequently seen in the endocardium of the mid-cavity segments (4.2 ± 4.4 i.f.v. in rats with TTS) (Table 1). Cardiomyocyte vacuolization was observed in LV and RV, except the epicardial layer of LV.

48 h post-ISO rare cardiomyocyte vacuolization was observed in 3 rats. In the whole heart of the first rat with privilege of phenomena in the central and endocardial layers while in the second and third rats in endocardium of apical and mid-cavity segments respectively. IE was most frequently observed in the endocardium of the apical region in 4/6 (66.6%) rats. In RV, IE was noted in 2/6 (33.3%) rats in the apical region of the heart and 1/6 (16.6%) rats in the mid-cavity and basal segments. The foci of infiltrating cells were larger, most numerous and were not only visible mainly in the central layer of the apical region (7.7 ± 4.5 i.f.v.) but also in endocardium of mid-cavity segments (4.3 ± 2.3 i.f.v.). In basal segments of the heart's foci were rather rare phenomena relatively most frequently observed in the central layer (0.8 ± 1.0 (Table 1). Statistically significant differences were noted in central layer in apical vs basal segments ($p = 0.0032$) and in endocardial layer in apical vs. basal segments ($p = 0.00024$) and in mid-cavital vs. basal segments ($p = 0.0483$) (Table 1).

72 h post-ISO foci seem to predominate in the apical region in central layer 8.5 ± 3.8 vs. 2.5 ± 1.6 in basal segments ($p = 0.0283$) (Table 1).

7 days post-ISO single foci were distinguishable with a maximum of 3.3±2.7 i.f.v. in apex.

The histopathological analysis of RV revealed (Fig. 4) that the mean number of foci was similar in all segments through all periods of time (Table 1). The maximum number of foci in the field of view was 8. The highest concentration of foci was observed in the papillary muscles.

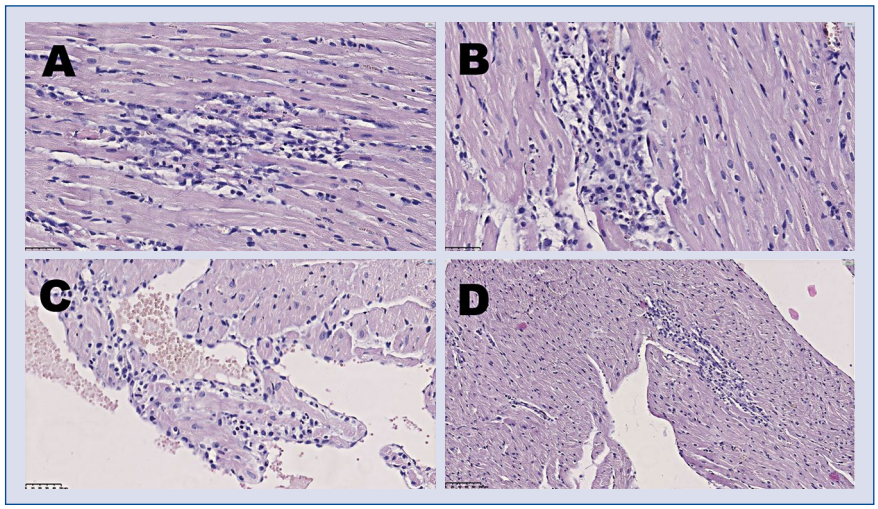

Figure 5. Histopathological abnormalities in female rats 48 h post isoprenaline (ISO) dose 200 mg/kg body weight administration without echocardiographical features of Takotsubo syndrome; **A.** Apical segment of left ventricle (LV). Focal inflammatory cell infiltration; **B.** Mid-cavity segment of LV. Focal inflammatory cell infiltration; **C.** Basal segment of LV. Focal inflammatory cells infiltration; **D.** Right ventricle. Focal inflammatory inflammatory cell infiltration.

Table 2. Comparison of the mean number of foci of cardiomyocyte necrosis/apoptosis and inflammatory cell infiltration between 150 mg/kg body weight and 200 mg/kg body weight isoprenaline injected female rats.

Segment of the heart	Localization	The mean number of foci (150 mg/kg vs. 200 mg/kg)	P
Apical	Central layer	7.7 ± 4.5 vs 3.6 ± 1.5	> 0.05
	Endocardial layer	5.8 ± 1.7 vs 2.8 ± 1.1	> 0.05
	Right ventricle	3.0 ± 1.5 vs. 3.0 ± 1.7	> 0.05
Mid-cavity	Central layer	3.8 ± 2.0 vs. 3.0 ± 1.4	> 0.05
	Endocardial layer	4.3 ± 2.3 vs. 3.4 ± 1.7	> 0.05
	Right ventricle	2.2 ± 1.5 vs. 2.4 ± 1.7	> 0.05
Basal	Central layer	0.8 ± 1.0 vs. 1.8 ± 1.9	> 0.05
	Endocardial layer	0.3 ± 0.8 vs. 1.2 ± 0.8	> 0.05
	Right ventricle	3.1 ± 1.6 vs. 2.2 ± 1.3	> 0.05

Histopathology: Rats without features of TTS in echocardiography (post-ISO 200 mg/kg bw)

Five female rats received ISO 200 mg/kg bw, none of them developed echocardiographical features of TTS. In the histopathological analysis, all hearts presented abnormalities. Features of inflammatory cell mobilization was evident in all layers of LV except the epicardium (Fig. 5). The number of foci with inflammatory cell infiltration was significantly less than in the group of rats with TTS induced with a 150 mg/kg bw dose, 48 h post-ISO, especially in the endocardium of the apical region 5.8 ± 1.7 vs. 2.8 ± 1.1 (p = 0.0084) (Table 2). IE was rarely seen but was present in 3/5 rats in the endocardial layer of the apical segments. Cardiomyocyte vacuolization was not observed.

Heart fibrosis in TTS

Trichorme blue staining revealed mild fibrosis typical for TTS in both acute and recovery phases (Fig. 6).

Discussion

There are a few animal based studies related to TTS and fewer still in female rats according to available research. The main findings concern the

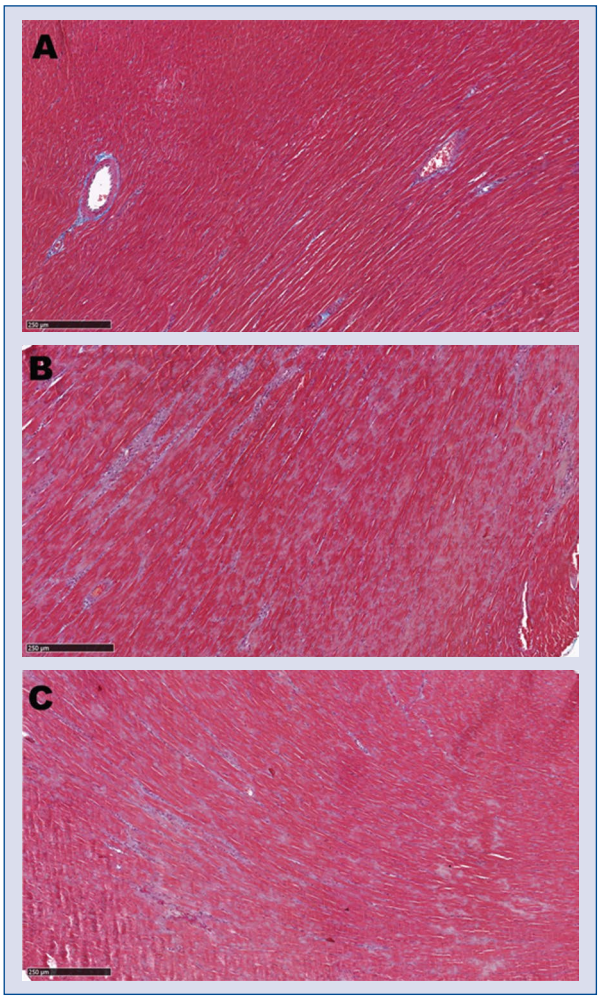

Figure 6. Trichrome blue staining revealed fibrosis; **A.** Control rat; **B.** Acute phase of Takotsubo syndrome — mild fibrosis; **C.** Recovery phase of Takotsubo syndrome — mild fibrosis.

characterization of ISO based female rat model of TTS. Histopathological analysis revealed that TTS is associated with multiple, singles cardiomyocytes apoptosis/necrosis with inflammatory and fibroblast-like cells infiltrations, mainly in the central muscle layer with apical-basal gradient. TTS presents as a disease of the whole heart with the strongest histopathological and echocardiographic expression in LV apex and RV.

In the present study both low (50–100 mg/kg bw) and high (200 mg/kg bw) doses of ISO were ineffective in TTS induction. Shao et al. [13] tested male Sprague Dawley rats with different doses of ISO. An ISO dose of 25 mg/kg bw did not induce apical ballooning [13]. High frequency TTS occurred at an ISO dose of 50 mg/kg bw, and the incidence did not increase with higher doses of ISO (100–600 mg/kg bw). In the current study the optimum dose of ISO that induced TTS in adult female rats appeared to be 150 mg/kg bw with effectiveness 77.77%. All TTS cases presented apical akinesia. Shao et al. [13] noticed atypical basal and midmyocardial akinesia with preservation of apical contractility in four rats, two treated with an ISO dose of 150 mg/kg bw and two with 450 mg/kg bw. Redfors et al. [17] showed that not only isoprenaline but all other catecholamines (epinephrine, norepinephrine, dopamine, phenylephrine) may induce TTS. They presented that an ISO dose of 50 mg/kg bw induced mainly typical apical akinesia while substances with alfa-adrenergic activation, such as epinephrine, mainly revers-TTS [17].

The total mortality was 6.12% and in the 150 mg/kg/ bw group 3.7% and was lower than reported, occurring in all rats in the first 24 h post-ISO. Shao et al. [13] observed a high mortality associated with ISO doses ≥ 300 mg/kg bw. At doses ≤ 150 mg/kg bw, death occurred only in male rats that developed severe TTS with akinetic area > 30% of total LV area. All deaths were noticed 48 hours post-ISO and concerned 7 (29.2%) animals. Seven-day mortality was 50% in rats that received 50 mg/kg bw [13].

Little is known about cardiac histopathology in TTS. In humans, there are a few case reports and short series of patients that underwent heart biopsy. Iacucci et al. [18] analyzed a cardiovascular magnetic resonance with heart biopsies in TTS. They observed that the severity of edema was directly proportional to the wall abnormality and low ejection fraction in patients and they also noticed inflammatory cell presence and disrupted myofibres. In a patient that died in the course of TTS, multiple necrotic lesion, monocytes and neutrophils infiltration, as well as hemorrhages were distinguished [19]. Shao et al. [13] reported lipotoxicity with lipid accumulation in the akinetic region that was resolved with the recovery of wall motion abnormalities. Sachdeva et al. [20] in the male rat TTS model with subcutaneous ISO administration presented multiple foci of necrosis scattered among the normal myofibres, mononuclear cell infiltration, and profuse IE in the apical-midventricular region of both ventricles. Moreover, in the biopsied myocardium of 8 females, catecholamine induced apoptosis of the endothelial cells of coronary microvessels was observed and was indicated as the missing link between stress and TTS.

In the present study, focal singles cardiomyocyte necrosis/apoptosis was only seen 24 h post-ISO. Vacuolization of cardiomyocytes was characteristic for the acute phase. IE was typical 24 h post-ISO and concerned all segments of RV

and LV except the epicardial zone. IE gradually diminished up to 48 h post-ISO, and finally was not distinguishable 72 h post-ISO. Because of a transient character of IE and persistence of motion abnormalities, even throughout 7 days, the hypothesis raised by Iacucci et al. [18] concerning the association between edema and motion abnormalities needs further evaluation. The features of vascularization, inflammatory and fibroblast-like cell mobilization were visible. The number and size of foci of inflammatory cell infiltrations increased from 24 h to 72 h post-ISO but were smaller than presented in the study of Sachdeva et al. [20] where the foci affected even the full thickness of LV. The apical-basal gradient of foci 24, 48, 72 h post-ISO based on the mean number of foci resemble the β-adrenoreceptors apical-basal gradient with the most numerous foci similar to β-adrenoreceptors accumulation in the apical region. Foci were the most numerous in central and endocardial heart muscle layers, rarely appearing in epicardial zone. In the foci TLR2, TLR4, TLR6 positive mononuclear cells and TLR4CD68 as well as TLR6CD68 positive cells were distinguishable [21]. Apoptosis concerned singles cardiomyocytes 24 h post-ISO, inflammatory cells in the whole course of TTS, and endothelial cells of the vessels 7 days post-ISO [21]. Moreover 7 days post-ISO a rare foci of inflammation with mild fibrosis was observed and the features of cardiomyocyte hypertrophy were recognized. The features of cardiomyocyte hypertrophy may be explained by the activation of β1 receptors that leads to phosphorylation of the L-type calcium channel and calcineurin signaling activation that leads to hypertrophy [22]. TLR4 expression in cardiomyocytes was previously documented [21]. Timmers et al. [23] observed that TLR4 defectiveness was associated with a reduction of interstitial fibrosis and cardiac hypertrophy in the non-infarcted area. TLR4 pathway may play relevant role in TTS. Both echocardiographic and histopathological features of TTS persisted longer in female rat model than in male rats as was reported in the literature by Shao et al. [13].

In the current study, female rats were used. Estrogen receptors are expressed in the cardiomyocytes and can directly act to reduce reactivity of the heart to catecholamines [24]. Ueyama et al. [25] presented that reduction of estrogen levels may explain the high incidence of TTS in ovariectomized (OVX) rats in comparison with estradiol-supplemented OVX animals. Thawornkaiwong et al. [26] showed upregulation of β1-adrenoreceptors in OVX rat hearts and proved that estrogen/progesterone supplementation reversed these changes. A lack of estrogen replacement in the postmenopausal state may predispose women to TTS [27].

Conclusions

In the female rat model of apical ballooning induced by a single dose of ISO intraperitoneal administration, TTS presents as a disorder of the single cardiomyocytes of both ventricles with a different prevalence between apical and basal segments, mainly in the central muscle layer and with significant inflammatory reaction.

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REVIEW ARTICLE

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Can we have a rationalized selection of intra-aortic balloon pump, Impella, and extracorporeal membrane oxygenation in the catheterization laboratory?

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Abstract

Cardiac assistance represents an emerging issue in cardiovascular medicine. The evolution of invasive cardiology techniques is making the catheterization laboratory one of the main hospital sites where implantation of percutaneous ventricular assistance devices (PVADs) is discussed and performed. Among available PVADs, intra-aortic balloon pump (IABP), Impella, and extracorporeal membrane oxygenation (ECMO) are the most popular and offer completely different levels and ways to assist critical patients. The main settings calling for PVAD consideration in the catheterization laboratory are clinically indicated high-risk patients (CHIP) undergoing percutaneous coronary intervention (PCI) and patients with cardiogenic shock or refractory cardiac arrest.

In CHIP, PVAD serves the purpose of preventing hemodynamic collapse during PCI. This may also allow more extensive revascularizations and higher quality revascularization plans (imaging use, debulking, stent result optimization). IABP or Impella are more commonly selected whereas ECMO is seldom considered as a third option for highly selected patients. The "elective" nature of CHIP-PCI should allow careful procedure planning (peripheral artery disease assessment, access site selection and management) in order to minimize vascular/bleeding complications.

Cardiogenic shock is still associated with high mortality rates, and PVAD theoretically offers further recovery chances. The lack of benefit observed with systematic IABP use is currently prompting consideration of the roles of Impella and ECMO. Prolonged assistance is often needed. Thus, team decisions and shared protocols for PVAD selection have to be promoted, taking into consideration available resources and operators' skills.

In this paper, we critically review the available data in the field and highlight the possible decision-making hubs that catheterization-laboratory teams may consider in order to rationalize PVAD selection.
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Key words: extracorporeal membrane oxygenation, Impella, intra-aortic balloon pump, percutaneous ventricular assist device, personalized medicine

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Introduction

The management of critically ill cardiac patients has aroused great interest in recent years. Percutaneous coronary intervention (PCI) techniques have expanded and gained respect as a valuable alternative to cardiac surgery in patients with complex coronary anatomy and high surgical risk. Given an aging population and improved treatments for chronic conditions and comorbidities, the high-risk PCI population, presenting with both stable and unstable conditions, is expanding in the catheterization laboratories. In parallel, the recognized benefit of coronary angiography and urgent myocardial revascularization in patients with critical clinical conditions like cardiogenic shock or refractory cardiac arrest put access to a catheterization laboratory in the pipeline of contemporary managing algorithms. This has raised interest in the search for the best management of patients with critical hemodynamic conditions.

The two conditions of PCI in clinically indicated high-risk patients (CHIP) and cardiogenic shock (CS) or refractory cardiac arrest, despite their completely different nature, share the characteristics of raising discussion about the possibility to benefit from hemodynamic support devices. For instance, this issue is particularly burning in the catheterization laboratory because such patient subsets systematically receive diagnostic and interventional procedures during which hemodynamic deterioration may occur [1]. Among the available percutaneous ventricular assist device (PVAD) systems, three are widely used: intra-aortic balloon pump (IABP), Impella (Abiomed Inc., Danvers, MA), and extracorporeal membrane oxygenation (ECMO). A fourth PVAD, the TandemHeart, is limited by the need for trans-septal puncture and is routinely used only in a limited number of highly experienced centers. Accordingly, its adoption represents an option only in selected environments.

In this paper, we critically review the available data in the field and highlight, within the lack of strong clinical evidence, the possible decision-making hubs that are encountered when selecting IABP, Impella, and ECMO in both CHIP and CS.

High-risk PCI: Definition and hemodynamics

Currently, no univocal definition of high-risk PCI exists, and it represents a continuously evolving concept. The risk scores (EuroSCORE and Society of Thoracic Surgery [STS] score) were derived from studies in the surgical field, and such scores are currently used to detect patients at higher risk for surgical interventions [2]. At the same time, the high surgical risk also predicts complexity in the case of PCI. Not surprisingly, the surgical scores may also be used to provide a mortality stratification for patients undergoing PCI (with event rates being generally lower than with surgery) [3, 4].

In the field of high-risk PCI, procedural planning and technical issues need to be carefully assessed [5, 6] when dealing with patients with impaired left ventricular (LV) function. First, coronary flow blockage may impair hemodynamic stability throughout the procedure when the underlined territory is large and LV function is poor. Highly calcified lesions, bifurcations, chronic total occlusion, and multivessel disease may require multiple balloon dilatations, increasing the risk for prolonged myocardial ischemia and consequent hemodynamic collapse. Similar consequences may come from vessel dissections, distal embolization, and side-branch occlusion. As regards multivessel coronary artery disease, it has been demonstrated that an extensive revascularization [2, 7] may impact long-term prognosis and that Impella may offer strong and reliable LV support allowing more complex revascularization procedures as compared to IABP in patients without acute myocardial infarction (MI) [8]. Alongside this, the myocardium at risk as measured by British Cardiovascular Intervention Society (BCIS) Myocardial Jeopardy Score [9] can be included in the pre-procedural risk assessment [10] both to predict the risk of hemodynamic collapse [11] and to assess the final revascularization extent through the BCIS Revascularization Index [10]. As regards LV function, no definite cut-off exists to indicate the need for any PVAD. However, reduced LV function increases the likelihood of hemodynamic instability during complex PCI procedures [12]. Finally, LV end-diastolic pressure represents an easy-to-obtain invasive measure of cardiac compensation and has been demonstrated to significantly stratify mortality in invasively managed acute coronary syndromes [13]. In this regard, an accurate evaluation of diastolic function in the preprocedural setting might be of pivotal importance for risk stratification, alongside LV systolic function (Table 1).

In such a scenario, LV support may reduce LV filling pressures and prevent critical cardiac output decrease. Such "LV unloading" is recognized to

Table 1. Echocardiographic features to consider in percutaneous ventricular assist device (PVAD) decision-making.

	Value	Notes
Systolic LV function		
LV ejection fraction	< 35%	
	> 35% with large amount of myocardium at risk (Jeopardy score)	Consider PVAD also for normal ejection fraction with indirect signs of reduced cardiac output (low LVOT VTI) or other signs of LV dysfunction (i.e. global longitudinal strain indicating severe longitudinal dysfunction)
LVOT VTI	< 15 cm	
Diastolic LV function		
E/A ratio	E<A velocity: abnormal diastolic function	For E/E' values between 10 and 15 add other parameters (pulmonary vein PW Doppler, color M-mode propagation velocity, B-lines at lung ultrasound) Pre-procedural assessment of LV filling pressure allows to: 1) choose among different PVADs; 2) consider LV venting strategies for VA-ECMO; 3) adequately plan weaning strategies
	E>A velocity: restrictive physiology	
E/E' ratio	≥ 15 (septal or average) indicates elevated LAP	
E deceleration time	> 240 ms: abnormal diastolic function	
	< 160 ms: restrictive physiology	
IVRT	> 110 ms: abnormal diastolic function	
	< 60 ms: restrictive physiology	
RV function		
TAPSE	< 15 mm	In case of reduced RV function, consider biventricular systems (ECMO, Bipella)
S wave TDI	< 9 cm/s	
Fractional area change	< 35%	
Valvular heart disease		
Mitral/aortic	Assess and quantify regurgitation or stenosis	Check for contraindications
LV thrombus	Look for intraventricular thrombus if Impella is planned	

LAP — left atrial pressure; LV — left ventricle; LVOT — left ventricle outflow tract; VTI — velocity time integral; IVRT — isovolumic relaxation time; RV — right ventricle; TAPSE — tricuspid annular plane systolic excursion; TDI — tissue Doppler imaging; VA-ECMO — veno-arterial extracorporeal membrane oxygenation

limit infarct size in experimental canine models [14, 15] and to avoid hemodynamic collapse when multiple angioplasty-balloon inflations are needed [16].

On the basis of this evidence, PVAD might be considered a valuable approach to move from the concept of PCI performed accepting high risk ("high-risk PCI") to that of PCI performed with the help of devices that may reduce hemodynamic-intolerance risk ("protected-PCI") [6].

PVADs and high-risk PCI

Intra-aortic balloon pump

The IABP represents the traditional method for mechanical circulatory support and was first used by Kantrowitz et al. [17] in 1968 for the management of acute MI complicated by CS. It works by deflating during systole (QRS-T segment) and inflating during diastole (T-P segment). In this way diastolic augmentation during inflation contributes

to coronary, cerebral, and systemic circulation. Diastolic pressure augmentation during balloon inflation is influenced by Weber and Janicki [18]:

— balloon position: the closer the IABP is positioned to the aortic valve, the greater the diastolic pressure elevation;
— balloon volume: when the balloon volume equalizes the stroke volume, then the diastolic augmentation is maximized;
— balloon diameter and occlusivity: the greatest augmentation occurs with complete aortic occlusion. The size of the aorta is related to the patient size, age, and weight. Usually, balloon dimensions are based on patient height. Different balloon volumes from 25 cc to 50 cc are available on the market, with 40 cc being the most commonly used;
— balloon configuration/timing;
— stroke volume: diastolic augmentation is maximized when stroke volume is equal to balloon volume. If stroke volume is very low (e.g. 25–30 mL) or very high (95–100 mL), augmentation will be limited;
— arterial pressure and heart rate.

There are several cardiovascular effects induced by IABP: it reduces the end-diastolic aortic pressure by up 30%, indicating systolic unloading; it decreases the LV wall tension; and it decreases the rate of LV pressure rise (dp/dt). There is controversial evidence on the degree of post-stenotic coronary blood flow augmentation achieved despite the increase in perfusion pressure. Some reports demonstrate no increase in coronary blood flow distal to critical stenosis [19, 20], whereas others demonstrated an increase of distal flow independent of any stenosis [21, 22].

The final effect of IABP is to lower the LV afterload, and to decrease myocardial oxygen demand (reducing systolic wall tension and increasing coronary perfusion pressure), thus improving the myocardial supply/demand balance. Finally, cardiac output increases because of the improved myocardial contractility as a result of the reduced afterload and of the possible increased coronary blood flow [23]. Currently, several IABP models produced by different manufacturers are available. Catheter size varies from 8 to 9 Fr, and some of them are provided with fiber-optic pressure sensing.

IABP and high-risk PCI

According to the current European guidelines, the role of IABP in the setting of high-risk PCI is still debated and unclear [24–26], whereas American Heart Association/American College of Cardiology (AHA/ACC) guidelines suggest that elective insertion of an appropriate hemodynamic support device, as an adjunct to PCI, may be reasonable in carefully selected high-risk patients (Class IIb, LoE: C) [27], although no support device is specified and selection criteria for high-risk patients are not defined (Table 2)

Past clinical experience supports the usefulness of elective IABP for high-risk PCI [28–30]. However, data from the National Cardiovascular Data Registry (NCDR) found no difference in overall mortality with use of the IABP for high-risk PCI. The registry enrolled almost 19,000 "high-risk" patients treated with IABP-supported PCI [31]. Of note, alongside patients with unprotected left main artery as the target vessel or with ST elevation, the study population included also those with CS. Routine prophylactic use of IABP in high-risk PCI has definitely come into question following the results of a large randomized trial [32]. A total of 301 patients undergoing high-risk PCI, defined as severe LV systolic dysfunction (left ventricular ejection fraction [LVEF] < 30%) and extensive coronary artery disease, were randomized in the BCIS-1 trial to either "planned" IABP or "no planned" IABP prior to PCI. No difference was reported in the primary endpoint of major adverse cardiac and cerebrovascular events at 28 days, despite a marked reduction in procedural complications. In addition, bleeding and access-site complications trended higher with routine IABP use. Mortality was not different at 6 months but was significantly reduced at long-term follow-up (median of 51 months), with a relative reduction of 34% of all-cause death in the "planned" IABP group [33]. Because the trial was not powered to reveal a mortality difference, these results can only be deemed hypothesis generating. However, they suggest the importance of a proper procedure planning in such critical patients or, given the rate of bailout IABP, an initial strategy of standby IABP for PCI in those patients with compromised myocardial reserve, and extensive coronary artery disease would therefore seem a reasonable strategy.

Independently of the scientific data, low costs, wide availability, ease of use, and low invasiveness make IABP an important tool in PCI clinical practice. Accordingly, IABP can be considered a valuable option in all situations requiring a low-to-moderate grade of LV support (Fig. 1).

Of note, because anytime cardiac assistance is not electively used, it should be promptly inserted on bail-out; when high-suspicion of

Table 2. Use of percutaneous ventricular assist device (PVAD) in high-risk percutaneous coronary intervention (PCI) according to international guidelines.

PVAD	Clinical setting	Guidelines	Recommendation class	Level of evidence	Recommendation
MECHANICAL SUPPORT	ST-segment elevation myocardial infarction	STEMI ESC 2017			Mechanical circulatory support may be considered as a rescue therapy in order to stabilize the patients and preserve organ perfusion (oxygenation) as a bridge to recovery of myocardial function, cardiac transplantation, or even left ventricle assist device destination therapy on an individual basis
	High-risk patients*	PCI ACCF/ /AHA/SCAI 2011	IIb	C	Elective insertion of an appropriate hemodynamic support device as an adjunct to PCI may be reasonable in carefully selected high-risk patients

*"High-risk patients may include those undergoing unprotected left main or last-remaining-conduit PCI, those with severely depressed ejection fraction undergoing PCI of a vessel supplying a large territory, and/or those with cardiogenic shock. Patient risk, hemodynamic support, ease of application/removal, and operator and laboratory expertise are all factors involved in consideration of use of these devices".

Classes of recommendations:
I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective
IIa: Weight of evidence/opinion is in favor of usefulness/efficacy
IIb: Usefulness/efficacy is less well established by evidence/opinion
III: Evidence or general agreement that the given treatment or procedure is not useful/effective, and in some cases may be harmful
Level of evidence:
A: data derived from multiple randomized clinical trials or meta-analyses
B: data derived from single randomized clinical trial or large non-randomized studies
C: consensus of opinion of the experts and/or small studies, retrospective studies, registries

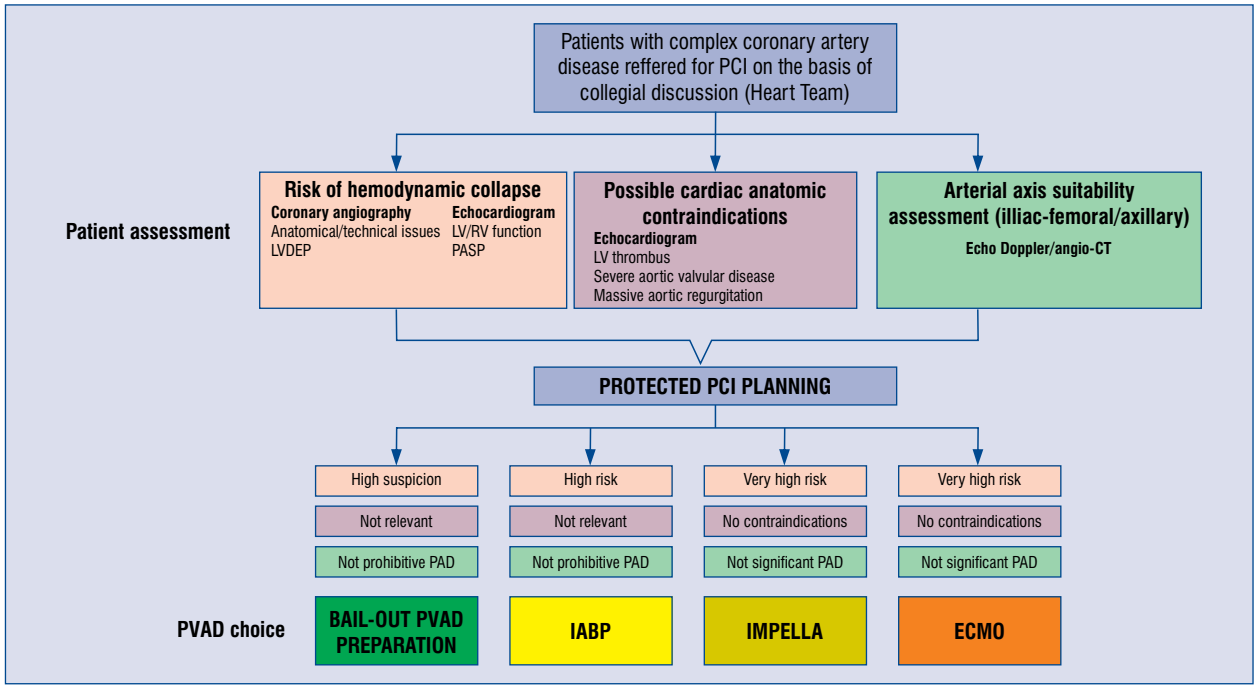


Figure 1. Proposed pre-procedural assessment and percutaneous ventricular assistance device (PVAD) choice in the context of high-risk percutaneous coronary intervention (PCI); LVEDP — left ventricle end-diastolic pressure; PASP — pulmonary artery systolic pressure; PAD — peripheral artery disease; CT — computed tomography; IABP — intra-aortic-balloon pump; LV — left ventricle; RV — right ventricle; ECMO — extracorporeal membrane oxygention.

hemodynamic collapse exists, a safe approach would be to prepare for PVAD insertion. To do this, the femoral access can be effectively gained and a small-bore sheath (e.g. 5 Fr) inserted to facilitate easy and fast exchange if needed. Alongside access site preparation, the device and the team involved (e.g. operators, technicians, nurses) should be prepared for bail-out PVAD placement as well (Fig. 1).

Percutaneous LV-to-aorta circulatory support: Impella

The Impella (Impella, Abiomed Inc., Danvers, MA) is a microaxial pump delivering blood from the LV forward into the ascending aorta. It is inserted through the femoral route (13–14 Fr) or it can be placed surgically through the axillary artery. Once the access site has been achieved [34], it is advanced from the aorta into the LV. Because it requires aortic valve crossing, moderate-to-severe aortic valve disease is a contraindication for its use. It is connected to an "Automated Impella Controller", which provides a step-by-step guide to the device implantation and controls the Impella catheter performance, monitors for alarms, and displays real-time hemodynamic and catheter position information. The latest updates have implemented the "Smart Assist Platform", providing useful information about the position of the Impella, to facilitate its repositioning in intensive care units without the need for imaging, and about hemodynamic features (LV end-diastolic pressure, mean arterial pressure, and cardiac power output).

According to the manufacturers' instructions for authors, the device is intended for short-term use (up to 4 days in the case of cardiogenic shock), although the new "PROPELLA" concept in the context of myocarditis has increased the time of support [35]. The device output may vary from 2.5 to 5.0 L/min, according to the different pumps. The main Impella pump characteristics have been summarized elsewhere [33].

The Impella increases the mean arterial pressure, cardiac output, and systemic and coronary perfusion. Its main effect is a significant LV unloading, resulting in filling pressure decrease and afterload. The direct unloading of LV and the coronary blood flow increase lead to significant oxygen supply improvement and reduction of myocardial oxygen consumption, with cardio protective effects. The final native stroke volume can be reduced, although the device replaces the pump function.

Impella and high-risk PCI

The introduction of the Impella support device has brought a significant change in the field of high-risk PCI, allowing highly complex procedures for patients deemed not suitable for surgery and at high risk for intraprocedural hemodynamic collapse (Table 2) [36].

Most of the data about the use of the Impella in the context of high-risk PCI come from the PROTECT II trial [8]. A total of 448 patients were randomized to IABP or Impella 2.5 for elective high-risk PCI. Inclusion criteria were similar to those of BCIS-1 although the primary end-point was made of a composite of heterogeneous adverse events, and patients with ST segment elevation myocardial infarction (STEMI) within 24 hours or not normalized myocardial enzymes were excluded from the study. Of note, the trial was interrupted due to futility in the prespecified endpoints. At 90-day follow-up the major adverse cardiac event occurrence was significantly lower in the Impella group as compared to the IABP group ($p = 0.023$ in the "per protocol" analysis, $p = 0.066$ in the "intention-to-treat" analysis). Moreover, the different use of adjunctive devices (e.g. Rotablator) and the higher complexity of the Impella-group patients suggests different PCI planning and management between the two groups. Finally, the overall duration of support was significantly lower in the Impella group, with only 6% of patients being discharged from the cath lab on Impella, as compared to 37% of patients keeping the IABP after the end of the procedure.

Alongside this, the two largest published series, the multicenter Europella and USpella registries, provided new data regarding the real-world practice [37, 38]. The baseline characteristics of the 144 patients in the Europella Registry suggest that these patients were indeed at high risk: almost two third had an LVEF less than 40%, 39% had more than three target lesions, 53% underwent left main coronary artery PCI, and 17% had intervention on a last remaining patent vessel. The logistic EuroScore was 15 ± 12.2, which further indicated the high-risk nature of this population. Despite this, overall mortality was only 5.5% at 30 days. The multicenter USpella Registry included results on 178 high-risk patients undergoing Impella-supported PCI. Similarly to the Europella, 62% had an LVEF less than 30% before intervention. Results showed an 8% rate of 30-day major adverse cardiac events, while survival was 96% at 30 days, 91% at 6 months, and 88% at 1 year. In addition, only 30% of patients remained in New York Heart

Association (NYHA) class III or IV heart failure, consistent with an absolute increase in mean ejection fraction from 31% to 37%. This latter improvement resulted in a 29% reduction in the anticipated need for implantable cardioverter defibrillators because the percentage of patients with an ejection fraction less than 30% was reduced from 62% to 44% [15].

These data were consistent with those coming from a recent large Italian registry [10]. It included 86 patients undergoing high-risk PCI with Impella support. After 14 months of follow-up the all-cause death was 10%. Of note, at follow-up a 205% increase in patients with LVEF > 35% was observed with BCIS Jeopardy Score Revascularization Index, significantly affecting long-term survival. Based on the current available data, the Impella should be considered in cases where the risk of hemodynamic collapse is very high and when no device contraindications are met (Fig. 1).

Percutaneous ECMO

ECMO has been increasingly used over the past decade to support patients with cardiopulmonary collapse [1]. Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) provides cardiopulmonary support for patients in profound CS as a bridge to the following:

— myocardial recovery;
— durable mechanical circulatory support;
— heart transplant.

In a VA-ECMO circuit, deoxygenated blood is pulled from the venous circulation by a pump via a large-bore cannula (21–23 Fr) inserted through the femoral vein. Blood passes through the pump into an oxygenator where gas exchange occurs. Finally, oxygenated blood returns via another large-bore cannula (15–17 Fr) to the arterial circulation, usually inserted into the common femoral artery.

In order to reduce the risk of critical limb ischemia in the cannulated femoral artery, distal perfusion catheters/sheath introducers, which direct a proportion of the returned oxygenated blood flow from the ECMO circuit to the distal limb, are positioned [39]. In this way it provides continuous, non-pulsatile output (> 4.5 L/min) and adequate blood oxygenation. ECMO is also known to determine a significant increase in LV pre- and afterload and in myocardial oxygen consumption that may limit its cardio protective effect [21].

During ECMO support, vasodilators might reduce afterload and LV end-diastolic pressure, while inotropes can increase contractility. In order to achieve LV unloading IABP [40], an Impella [41], a surgical LV vent, or a percutaneous balloon atrioseptostomy [42] might be added as adjunctive devices.

Due to huge cannula sizes, the implantation procedure requires considerable technical skill, and vascular/bleeding complications are common. Recent experience has started to highlight percutaneous implantation techniques as a promising way to increase ECMO safety. In particular, a recent propensity-matched analysis compared percutaneous versus surgical VA-ECMO showed significantly higher survival in the percutaneous groups and lower cannulation site infection. However, a significantly higher rate of vascular complications after cannula removal was reported, mainly represented by persistent bleeding requiring surgical repair [43].

ECMO and high-risk PCI

ECMO experience for high-risk PCI is limited to a few monocentric observational studies or individual case reports [44, 45]. They all demonstrate feasibility and efficacy of ECMO, although vascular complications and bleedings may represent a major concern. A recent case series included 5 patients undergoing elective high-risk PCI with ECMO support [46]. The mean LVEF was 26.6 ± 18.0%. Most procedures were unprotected left main PCIs, and there was only one chronic total occlusion through the last remaining conduit. All PCIs were successful, and ECMO was successfully weaned in all cases, with the duration of support being < 24 hours in 4 cases. There was no occurrence of in-hospital and 1-year major adverse events. However, 1 patient required femoral artery surgical repair, and 2 patients required general anesthesia. The limited experience and the ECMO invasiveness call for very selective use in the setting of high-risk PCI when the need for assistance is felt to be mandatory, anatomic contraindications for Impella (or its unavailability) are present, and vascular axes are suitable for insertion (Fig. 1).

Cardiogenic shock

Currently, no univocal definition exists, and there are slight differences among the current European guidelines and the recent trials (Table 3) [47–50]. The recent Heart Failure Association position statement defined CS as a syndrome caused by primary cardiovascular disorder in which inadequate cardiac output results in a life-threatening state of tissue hypoperfusion associated with impairment of tissue oxygen metabolism and hyperlactatemia, which, depending on its

Table 3. Cardiogenic shock definitions according to European guidelines and recent clinical trials.

ESC Guidelines [47]	IABP SHOCK II [48]	SHOCK TRIAL [49]
SBP ≤ 90 mmHg with adequate blood volume and clinical or laboratory signs of hypoperfusion	SBP ≤ 90 mmHg for at least 30 min or need for catecholamine in order to achieve SBP ≥ 90 mmHg	SBP ≤ 90 mmHg for at least 30 min or need for support in order to achieve SBP ≥ 90 mmHg
	+	+
Hypoperfusion: clinical signs	**Pulmonary congestion signs**	**Hypoperfusion signs:**
Cold extremities		Cold skin
Oliguria		Diuresis < 30 mL/h
Mental confusion		
Dizziness		
	+	+
Hypoperfusion: lab signs	**Hypoperfusion signs:**	**Hemodynamic criteria**
Metabolic acidosis	Altered mental status	CI ≤ 2.2 L/min/m
Blood lactates increase	Cold skin	PCWP ≥ 15 mmHg
Blood creatinine increase	Diuresis < 30 mL/h	
	Lactates > 2.0 mmol/L	

SBP — systolic blood pressure; CI — cardiac index; PCWP — pulmonary capillary wedge pressure

severity, may result in multi-organ dysfunction and death [51].

Recently, the Society Cardiovascular Angiography and Intervention introduced a new classification in five stages for CS [52]:

- A: "at risk": patient without signs/symptoms of CS but at risk for it;
- B: "beginning": patient with hypotension and tachycardia, without hypoperfusion;
- C: "classic": when also hypoperfusion occurs and inotropes, vasopressors, or mechanical support are needed;
- D: "deteriorating": in cases of poor response to treatment in level "C" and worsening conditions;
- E: "extremis": patient with circulatory collapse with ongoing cardiopulmonary resuscitation or on ECMO.

Cardiogenic shock is caused more frequently by LV dysfunction, with MI accounting for more than 80% of cases of CS. In some cases, also right ventricular dysfunction or bi-ventricular dysfunction are responsible for CS. In spite of new technological developments, technical PCI improvements, and pharmacological management changes, CS is still affected by high mortality.

The use of PVAD has already changed the CS natural history, and although scientific data are still controversial, their use is recommended in the current international guidelines (Table 4) [6, 18, 25, 26, 53, 54] and supported by many expert users [55].

Cardiogenic schock may rapidly become irreversible, and for this reason the timing of intervention might influence the efficacy of any device. Nowadays, many factors have been identified as potential mortality predictors in the setting of CS [56–58], and some patients with advanced CS are unlikely to recover even with a short time for intervention and with the strongest PVAD. For this reason, an important step for PVAD selection is represented by the early recognition of conditions defining the "futility" for the treatment.

PVADs in refractory cardiac arrest

The use of PVADs in specific situations such as refractory cardiac arrest is still controversial. Indeed, initial observational data about refractory cardiac arrest show the importance of early cardiac catheterization in comatose survivors without signs of STEMI [59]. Following this, AHA guidelines suggested emergent coronary angiogram for selected patients with cardiac arrest, who are comatose with electrical or hemodynamic instability [60].

However, those data were disproven by the more recent COACT trial [61, 62]: at 90 days and after 1-year follow-up, no significant differences in survival and major adverse cardiac events were found between patients undergoing immediate and delayed coronary angiography if signs of STEMI were not present. Around two thirds of the entire population had an underlying coronary artery disease, and only 30–40% of them underwent revascu-

Table 4. Use of percutaneous ventricular assist device (PVAD) in cardiogenic shock according to international guidelines.

PVAD	Clinical setting	Guidelines	Recommendation class	Level of evidence	Recommendation
IABP	Post MI CS	STEMI ACC/AHA 2013	IIa	B	Patients who do not quickly stabilize with pharmacological therapy
	Post MI CS	HF ESC 2016 STEMI ESC 2017 SCA NSTE ESC 2015	IIa	C	CS due to mechanical complications of MI
	CS	HF ESC 2016 STEMI ESC 2017 SCA NSTE ESC 2015	III	B	Routine use of IABP is not recommended
MECHANICAL SUPPORT	CS	HF ESC 2016	IIb	C	May be considered in refractory CS depending on patient age, comorbidities, and neurological function
		HF ACC/AHA 2013	IIa	B	
	Post MI CS	Myocardial Revascularization ESC 2018	IIb	C	In selected patients with acute coronary syndrome and CS, mechanical circulatory support may be considered, depending on patient age, comorbidities, neurological function, and the prospects for long-term survival and predicted quality of life

Classes of recommendations and levels of evidence as for Table 1. CS — cardiogenic shock; IABP — intra-aortic balloon pump; MI — myocardial infarction

larization treatment (either PCI or coronary artery bypass grafting), while conservative management was selected for the remaining 60–70%. Interestingly, CS was responsible for 11.7% and 8.4% of deaths in the immediate invasive and delayed invasive groups, respectively. Multi-organ failure leading to death occurred in 8.5% and 14.5% of immediate invasive and delayed invasive patients, respectively. Moreover, around 2–3% of screened patients were excluded due to hemodynamic instability unresponsive to medical therapy and some patients switched from the delayed to the immediate group due to shock development. These data raise the question about the possible usefulness of PVADs in the setting of cardiac arrest without STEMI signs.

On the other hand, among patients experiencing cardiac arrest in the context of STEMI, CS is more likely to occur as compared to those without cardiac arrest (36.7% vs. 5.9%, $p < 0.001$) [63]. Moreover, those with CS and cardiac arrest show higher mortality than those without cardiac arrest (47.3% vs. 25.1%, $p < 0.001$). Overall, data suggest that PVADs should be considered in cases of cardiac arrest independently of diagnosis at admission (ischemic or not), although no data suggesting who might benefit more are currently available.

The AHA Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care published in 2010 indicate that ECMO may be considered in settings where it is readily available, blood flow interruption following arrest is brief, and the underlying condition leading to arrest is reversible [64]. However, the 2019 focus update does not recommend the routine use of ECMO for patients with cardiac arrest [65].

The most important outcome determinant in the context of cardiac arrest is represented by the time to chest compression that should begin immediately or at the latest within 5 min [66]. Following cardiac arrest and cardiopulmonary resuscitation (CPR) initiation, the ECMO team should be alerted and already prepared in the very early phases: in a propensity-matched analysis, ECMO implantation within 21 min of CPR initiation in out-of-hospital cardiac arrest patients provided better neurological outcomes [67]. Such data support early activation

of the ECMO team and suggest avoidance of refractory cardiac arrest onset (defined as the lack of return of spontaneous circulation after 30 min of appropriate CPR in the absence of hypothermia), although previous data report beneficial effects also in prolonged CPR and delayed ECMO implantation [68–70], provided that trained personnel are available [71]. In this perspective, time from cardiac arrest to CPR and then to ECMO is of utmost importance. Patients with initial rhythm of ventricular tachycardia/fibrillation and witnessed arrest are the best candidates for ECMO, while cases with asystole as initial rhythm, total cardiac arrest time > 60 min, and significant comorbidities affecting life-expectancy should be carefully evaluated by the Heart Team as possible futile cases.

Promising results have been demonstrated also with Impella CP or Impella CP+RP in small case series or case reports [72, 73].

Futility

Futility should always be taken into account when evaluating the best treatment option for cardiac arrest, especially when PVAD placement is required. Currently, a number of different scores have been proposed to predict the survival of patients under ECMO treatment after cardiac arrest, such as SAVE score [74], ENCOURAGE score [75], and the ECMO score [76].

Recently, a simple rule consisting in non-shockable rhythm, unwitnessed arrest, and age ≥ 80 years has been proposed to predict futile resuscitation for out-of-hospital cardiac arrest [77]. However, it seems a simplistic approach, and some other well-known survival predictors should probably be considered (e.g. no-flow duration, initial cardiac rhythm, presence of gasping, etc.). Additional considerations should address the time for ECMO center transfer (in case of centers without ECMO capabilities) if the predicted duration of needed support is compatible with available technology or if the optimal window for any PVAD has already expired and the patient's wishes should be considered. A recent Panel Expert paper proposed the following inclusion and exclusion criteria for ECMO therapy selection [78].

Inclusion criteria:

— age < 70 years;
— shockable rhythm as initial rhythm;
— witnessed arrest;
— bystander CPR within 5 min;
— failure to achieve return of spontaneous circulation within 5 min of CPR start.

Exclusion criteria:

— asystole as initial rhythm;
— unwitnessed arrest;
— total cardiac arrest time > 60 min;
— pre-existing severe neurological or systemic disease;
— contraindications to anticoagulation;
— acute aortic dissection;
— suspicion of shock due to hemorrhage of other non-cardiac causes;
— known "do not resuscitate" status.

However, a multidisciplinary (e.g. cardiologist, cardiac surgeon, heart failure specialist, intensivist, palliative care specialist, etc.) case-by-case decision-making process should be adopted whenever feasible [79].

PVADs in cardiogenic shock

The most used PVADs for the CS or for refractory cardiac arrest are the IABP, Impella, and ECMO (Fig. 2), sometimes combined (ECMO + Impella or IABP). PVAD are mainly used in this setting as a bridge to recovery, to decision, or, more rarely, to transplant.

IABP and cardiogenic shock

In the context of CS due to acute coronary syndrome, current European guidelines do not recommend the systematic use of IABP (Table 4). It should be considered only in cases of hemodynamic instability and cardiogenic shock due to acute coronary syndrome mechanical complications (Class IIa, LoE: C) and in those with acute severe myocarditis [6]. These guidelines are mainly based on the IABP-SHOCK II trial results, which randomized 600 patients with MI complicated by CS to routine IABP versus no routine IABP [80]. All patients were expected to undergo early revascularization. No difference in all-cause mortality (IABP group 39.7% vs. control group 41.7%, p = 0.69) or any secondary endpoints was found at 30-day and 12-month follow-up. Of note, in this trial, patients of the "no routine" IABP arm received IABP in 10% of cases, and for other mechanical support devices in as many as 7.4% of cases. Moreover, the mortality rate itself was relatively low as compared to the SHOCK trial (30-day mortality rate of 46.7%), making the study underpowered. In addition, the CS definition did not take into account cardiac index or wedge pressure, as compared to the SHOCK trial.

Recently, the 6-year follow-up confirmed the negative results for both the intention-to-treat and for the as-treated population. These data led to

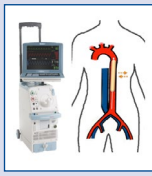
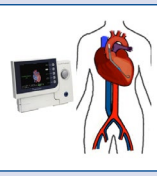
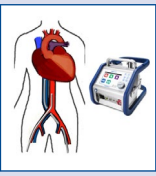
	Baseline	IABP	Impella		ECMO	IABP + ECMO	Impella + ECMO
							
French		8–9	13 (2.5)	14 (CP)	14–19 (A) 17–21 (V)	8–9 (IABP) + 14–19 (A) 17–21 (V)	13–14 (Impella) + 14–19 (A) 17–21 (V)
HR, bpm	100	100	100	100	100	100	100*
PCWP, mmHg	23	–4%	–9%	–13%	+17%	+13%	+9%*
AoP, mmHg	81/46 (61)	+2%	+8%	+15%	+28%	+31%	+39%*
CO, L/min	3.93	+5%	+13%	+28%	+43%	+48%	+60%*
CPO, watts	0.53	+7%	+21%	+34%	+81%	+91%	+118%*
PVA, mmHg × mL	4989	–3%	–7%	–13%	+16%	+14%	+7%*
CBF, mL/min/g	0.09	+10%	+10%	+20%	+40%	+50%	+70%*
Approved duration of assistance		No limitations (vascular complications increases after 2 days)	4 days (US) 5 days (EU)		Usually < 7 days [1] (poor survival if > 7 days)	See IABP and ECMO columns	See Impella and ECMO columns

Figure 2. Main characteristics and cardiac effects of intra-aortic balloon pump (IABP), Impella, extracorporeal membrane oxygenation (ECMO), and possible combinations strategies. All values are calculated with the Harvi Professor software; HR — heart rate; PCWP — pulmonary capillary wedge pressure; AoP — aortic pressure; CO — cardiac output; CPO — cardiac power output; PVA — pressure-volume area; CBF — coronary blood flow; *values are calculated considering Impella 2.5 combined with ECMO. For reference [1] see dedicated reference list.

a decrease in IABP use in favor of Impella and ECMO [81]. Accordingly, it makes sense to consider IABP in specific conditions like mechanical complications and earlier shock stages (pre-shock), as shown in Figure 3. It has been successfully used also in some cases of arrhythmic storm in ischemic patients [82, 83].

Impella and cardiogenic shock

Two randomized trials, ISAR-SHOCK [84] and IMPRESS [85], compared the use of IABP and Impella in patients experiencing acute MI complicated by CS, and no differences in the overall 30-day and 6-month mortality were found. Of note, both studies were underpowered for mortality. In the ISAR-SHOCK, Impella was implanted after coronary revascularization, while in the IMPRESS the implantation timing was left to the operators' choice, although more recent data suggest an early Impella positioning in patients with CS [86, 87]. Moreover, two recent meta-analyses confirmed the lack of benefit in terms of mortality, although an improvement in arterial lactate and mean blood pressure was found [88, 89]. In the specific scenario of acute myocarditis, the prolonged use of Impella, called "PROPELLA", has recently been proposed, but it still needs to be investigated on large groups of patients [34].

In general, available data do not support the routine use of Impella in patients with CS. Accordingly, its indication should be evaluated in the frame of local CS and careful case by case decisions [90]. In this regard, patients with severe LV dysfunction and persistent systemic hypoperfusion are those who may theoretically benefit from Impella LV support provided that futility has been ruled out (Fig. 3). Greater attention should be addressed to refractory CS or to biventricular dysfunction because those patients may not benefit from Impella left support alone, but they have been proposed to be approached using a combination of the Impella right and left system (Fig. 3) [91, 92].

ECMO and cardiogenic shock

In the field of CS, much broader experience has been gained with ECMO. It has been mostly studied in the context of CS following STEMI,

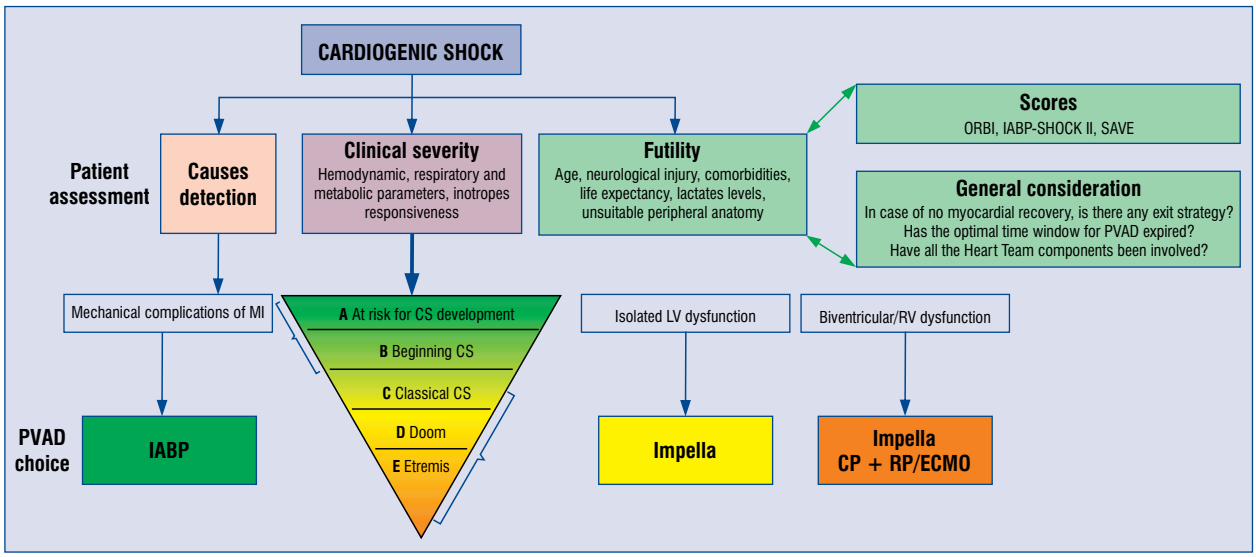


Figure 3. Proposed pre-procedural assessment and percutaneous ventricular assistance device (PVAD) choice in the context of cardiogenic shock (CS); IABP — intra-aortic balloon pump; MI — myocardial infarction; LV — left ventricle; RV — right ventricle; ECMO — extracorporeal membrane oxygenation.

acute myocarditis, post-cardiotomy, and in refractory cardiac arrest.

Retrospective data from Sheu et al. [93] and Chung et al. [94] demonstrated that the use of ECMO during primary PCI in patients admitted for STEMI complicated by CS may improve the 30-day outcome with an overall mortality of 43%.

In the setting of acute myocarditis complicated by CS, the ECMO has been used as a "bridge to recovery", with a survival rate around 70%, and the long-term outcomes were similar to those who experienced acute myocarditis without hemodynamic compromise [95–97].

A recent meta-analysis demonstrated a significant mortality benefit with ECMO in both cardiac arrest patients (n = 3098) and in patients with CS due to MI (n = 235). In cardiac arrest, the use of ECMO was associated with an absolute increase in 30-day survival of 13% compared with patients in whom ECMO was not used, whereas in CS ECMO showed a 33% greater 30-day survival compared with IABP but no difference when compared with TandemHeart/Impella [98].

Currently, the following trials are underway in order to improve CS management:

— ECLS-SHOCK (NCT03637205), ECMO--CS (NCT02301819), and EURO-SHOCK (NCT03813134): ECMO vs. control in severe CS complicating MI;
— DANGER (NCT01633502): Impella vs. control in severe CS complicating MI;
— REVERSE (NCT03431467), ECMO combined with Impella CP vs. ECMO alone in CS;
— PRAGUE OHCA (NCT01511666), ECMO vs. control in refractory out-of-hospital cardiac arrest.

While waiting for the results of such trials, ECMO should be regarded as an important tool in patients with more advanced CS and in those with biventricular failure (Fig. 3).

PVAD combination strategies

Although the use of ECMO is an established therapy option in severe CS, mortality is high. The lack of LV unloading and the increase of afterload are the main limitations for ECMO. These limitations together with the peculiar characteristics and the different hemodynamic effects of each device lead to combination strategies (Fig. 2) in order to improve outcomes in critical settings.

A recent meta-analysis demonstrated beneficial effects of LV unloading (achieved with IABP, Impella, or TandemHeart) on top of ECMO in the setting of CS [99]. The greatest source of data about the combination of IABP and ECMO is the Japanese database, which demonstrated a higher in-hospital and 28-day survival rate in those with both devices as compared to ECMO alone [100]. This might be explained by the counterbalance hemodynamic effect of IABP on ECMO, specifically afterload and myocardial oxygen demand reductions. Moreover, an additional positive IABP effect might be related to coronary perfusion increase. Similar results were achieved with the use of Impella on top of ECMO [41]. However, all available

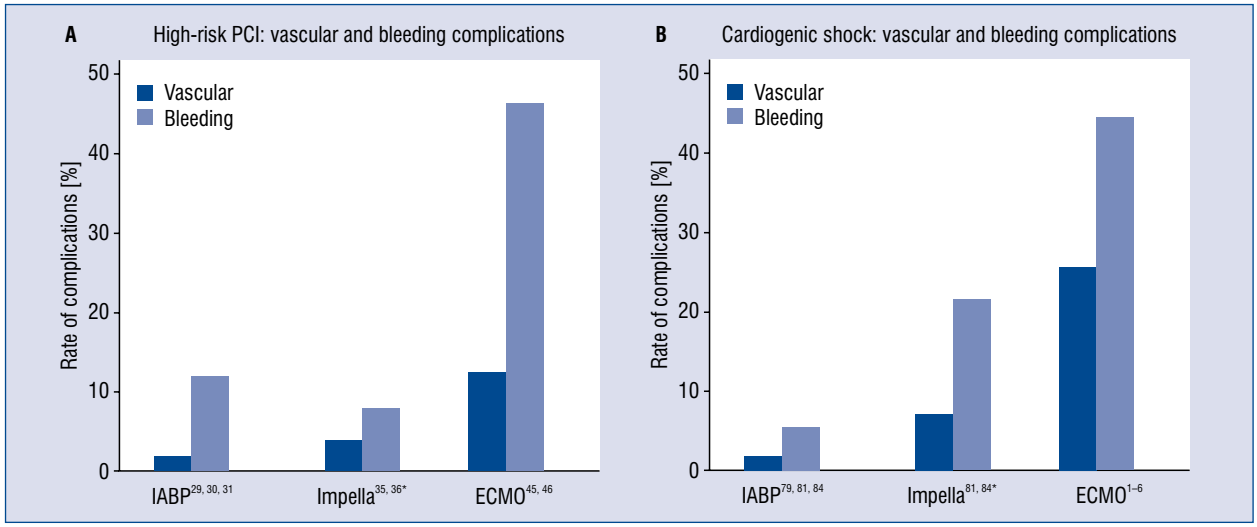


Figure 4. A. Access-site-related vascular and bleeding complication rate in high-risk percutaneous coronary intervention according to different percutaneous ventricular assist device (averaged mean value); **B.** Access-site-related vascular and bleeding complication rate in cardiogenic shock according to different percutaneous ventricular assist device (averaged mean value). Note: Major and minor vascular/bleeding complications are pooled together; PCI — percutaneous coronary intervention; IABP — intra-aortic balloon pump; ECMO — extracorporeal membrane oxygenation; *data from both Impella 2.5 and CP were considered. For references [1–6] see dedicated reference list.

data are retrospective, and possible complications should be considered when evaluating combination therapy (e.g. hemolysis, bleeding/vascular complications); consequently, randomized studies are needed to better investigate the beneficial effect of such strategies.

Finally, over the last few years, the Impella family has been enriched with the Impella RP pump. It delivers blood from the inferior vena cava (inlet area), through the cannula, to the pulmonary artery (outlet area). It has United States Food and Drug Administration approval and is indicated for providing right ventricular support for up to 14 days in patients developing acute right heart failure or decompensation following LV assist device implantation, MI, heart transplantation, or open-heart surgery. The main contraindications are right-side valvular heart disease, mural thrombus of the right atrium, or vena cava and anatomic conditions precluding insertion of the pump. Currently, data about the use of Impella RP and Bi-Pella are scarce. A retrospective study on 20 patients implanting the Bi-Pella demonstrated its feasibility and its efficacy, although CS causes were heterogeneous and in-hospital mortality was 50% [101].

At the same time, simultaneous initiation of support with Impella CP and Impella RP has been associated with improved survival outcomes as compared with staged initiation of support, and this would offer a stepwise weaning of univentricular or biventricular support [102].

Vascular and bleeding complications with PVADs

The large-bore size of the PVAD's sheath or cannula has the potential to induce access-site-related vascular complications. The occurrence of such vascular complications may cause acute anemia, transfusions, or urgent vascular surgery. Such events obviously have the potential to jeopardize the clinical course after effective high-risk PCI or during CS after initial effective stabilization. Thus, meticulous attention should be paid during the pre-PCI work-out, during the vascular access instauration, and during the hemostasis phase [33, 103]. Not surprisingly, data from the largest registries and trials show an increasing risk for vascular and bleeding issues correlated to the sheath size, with the IABP being the safest and the ECMO having the highest rate of complications (Fig. 4A, B). A recent sub-analysis of the CULPRIT-SHOCK trial showed that both ECMO and Impella treatments are predictors of bleeding events, and this, in turn, affects short-term survival probability [104].

In addition, when a second access is required (e.g. coronary angiography, PCI), the choice between contralateral femoral or radial access should be considered. A study comparing transradial

versus transfemoral secondary access for transcatheter aortic valve implantation has recently demonstrated a significant improvement in terms of vascular and bleeding complications in those using radial access as compared to femoral access [105]. Although no similar studies exist for PVADs, the experience from the transcatheter aortic valve implantation world might be applicable also to PVAD field. In this regard, a two-center experience with Impella and meticulous ancillary access and PVAD access hemostasis reported very promising safety results [10]. Consequently, the choice for the secondary access should be carefully evaluated according to the complexity of the procedure, the equipment available, and the operator's experience.

Conclusions

Percutaneous ventricular assistance devices are potentially useful tools for the management of critically ill patients, but many uncertainties exist regarding their clinical impact. Improved percutaneous techniques are making the catheterization laboratory an important location for PVAD implantation. Because different devices (with different mechanisms of action and anatomic requirement) are becoming more and more available, attempts to rationalize their selection in the context of local team expertise is pivotal.

Conflict of interest: Dr. Francesco Burzotta discloses to have been involved in advisory board meetings and having received speaker's fees from Abbott, Abiomed, Medtronic, and Biotronic. Dr. Cristina Aurigemma has been involved in advisory board activities by Abbott, Abiomed, Medtronic, and Biotronic. Dr. Carlo Trani discloses to have been involved in advisory board meetings and having received speaker's fees from Abbott, Abiomed, Medtronic, and Biotronic. Dr. Giulio Russo received fellowship training grant from EAPCI, sponsored by Edwards Life Sciences. Other authors have no conflicts of interest.

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The plague of unexpected drug recalls and the pandemic of falsified medications in cardiovascular medicine as a threat to patient safety and global public health: A brief review

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Abstract

Valsartan, losartan, and irbesartan, are widely used in the treatment strategies of cardiovascular medicine diseases, including hypertension and heart failure. Recently, many formulations for the aforementioned diseases contained active pharmaceutical ingredients and had been abruptly recalled from the market due to safety concerns mainly associated with unwanted impurities — nitrosamines, which are highly carcinogenic substances accidentally produced during manufacturing. Along with cardiovascular medications, formulations containing ranitidine were also recalled from the market. This poses a particular threat to public health due to the non-prescription status of these drugs. Regulatory authorities, including the Food and Drug Administration and European Medicines Agency among others, have taken action to minimize patient risk and improve the manufacturing quality as well as re-checking current guidelines and recommendations. While these steps are necessary to avoid further recalls, authorities should remember the growing concerns of patients regarding the safety and efficacy of pharmacotherapy. Apart from the genuine manufacturing mistakes mentioned above, falsified and counterfeit medications should be at the heart of global attention. The lack of a well-accepted definition of falsified/ /counterfeit medications has impeded political and scientific efforts to mitigate risk of this phenomenon. Falsified Medicines Directive should be considered the most pivotal legislation recently enacted to harmonize international cooperation. In summary, one should remember that only international and direct collaboration between patients, stakeholders, and authorities be considered a remedy for a pandemic of falsified medicines and plague of unexpected recalls due to safety concerns. (Cardiol J 2022; 29, 1: 133–139)

Key words: drug recalls, counterfeit drugs, pharmacovigilance, public health, angiotensin II type 1 receptor blockers

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Introduction: The complexities of pharmaceutical policy

One of the primary purposes of pharmaceutical policy is to ensure that patients have access to effective and safe medicines, safe not only in terms of acceptable risk associated with the treatment but also regarding the quality of drug formulation [1]. International differences, complex characteristics of the pharmaceutical market with sometimes conflicting objectives among stakeholders, and the rapid development of pharmaceutical and medical sciences have multiplied problems with good governance of the pharmaceutical market, and have constituted a significant challenge for contemporary authorities [2]. Moreover, any reasonable and well-planned pharmaceutical policy should minimize drug shortages — an issue that is increasingly difficult to cope with [3]. Drug re-importation in countries with a well-developed pharmaceutical market can, however, decrease the risk of drug shortages, and should be planned as part of pharmaceutical strategy authorized by governments responsible for public health [4, 5]. On the other hand, re-importation and parallel import, the latter known commonly in the European Union, can introduce drugs of unknown and substandard quality into the market, not to mention falsified and counterfeit medications [6].

Due to the fact that medications should have the highest possible quality, both governments and scientific bodies have created a set of legal and ethical guidelines aimed at ensuring patient safety [7, 8]. From the perspective of clinical importance, clinical drug effectiveness is tested extensively during clinical evaluations, mostly randomized controlled trials [9, 10]. When drugs are introduced into the market, post-authorization safety studies are conducted to detect adverse events, which cannot be noticed in pre-marketing phases, and must be established in epidemiological studies, predominantly in the field of pharmacoepidemiology [11].

While much is known about clinical significance, less attention has been paid to drug formulation, at least from the healthcare providers' perspective [12]. However, recent unintended drug recalls have forced us to reframe drug quality mostly as an international problem connecting all parties involved in drug production and distribution. Nagaich and Sadhna [13] listed several causes behind drug recalls, inter alia, label error in terms of declared dose, non-satisfactory stability, and, in recent cases, unwanted and potentially harmful substances. As a consequence, drug recalls due to safety issues may be one of the many causes responsible, at least temporarily, for drug shortages.

Thus, it is no surprise that effective mechanisms aimed at recalling a drug from the market, whenever necessary to ensure patient safety, must be implemented in harmony with a legal framework, and routine practice. The community pharmacy is importantly placed in this process and implies a core role of pharmacists in the protection of public health and patient safety [14]. Greater access to new media and the internet can facilitate this role significantly, on the other hand, and it may lead to an unwanted dissemination of false information and create unnecessary fear among chronically ill patients [15].

This paper aims to outline the recent drug recall events and their consequences for patient safety and global health and provide a brief commentary on the phenomenon of falsified medicines. Both issues are discussed, whenever possible, in the light of medications used in cardiovascular medicine, the treatment of hypertension, and heart failure. What should be stressed here is that the societal perspective remains at the core of deliberations and to emphasize public health implications from a plague of unexpected drug recalls and the pandemic of falsified medications, particularly with respect to medication adherence when it comes to trust in the medical profession and conventional medicine.

What are SSFFC? Drug recall versus drug withdrawal

Before talking about drug recalls based on safety issues, the acronym 'SSFFC' should be mentioned here (S — substandard, S — spurious, F — falsely labeled, F — falsified, C — counterfeit), as suggested by the World Health Organization (WHO) (Table 1). Although this classification seems to be useful, there is still no universally agreed definition of falsified/counterfeit drugs; thus, scientific deliberation and discussion are significantly impeded, which has also affected the international cooperation necessary to eliminate this phenomenon from the market.

Similarly, the WHO approach is determined to distinguish medicinal products that are intentionally falsified from substandard products mainly introduced into the market as the result of an unintentional mistake [16]. In 2017, the WHO decided to push for greater transparency and simplification of terminology. According to WHO, i) substandard medicinal products are those drugs manufactured 'out of specification'; ii) unregistered/unlicensed products are

Table 1. Substandard and Falsified Medicinal Products according to World Health Organization (2011) — summary [54].

Term	Definition
S — Substandard	Medicines produced not in line with specifications, including intentional and negligent mistakes, not including genuine manufacturing errors
S — Spurious	Products falsely labeled or intended to deceive; the term used mostly in South Asia
F — Falsely labelled	Genuine products with false packaging
F — Falsified	Products introduced into the market with deliberate intention to mimic original formulation and deceive stakeholders; definition widely used in European legal framework
C — Counterfeit	Violation of intellectual property rights, mostly used in the United States

produced and distributed against national regulation, and iii) falsified products 'intentionally' misrepresent their identity, composition or source' [17].

Additionally, drug recall should be recognized as a different concept from drug withdrawal, when drugs are removed from the market due to unwanted drug events. Until new studies are provided, a particular medication which should no longer be used by patients. This procedure is illustrated by the cases of valdecoxib and rofecoxib, nonsteroidal anti-inflammatory drugs previously widely used in rheumatoid arthritis, withdrawn from the market due to increased cardiovascular risk among patients [18].

Falsified medications: A global challenge for the pharmaceutical policy

Although this paper aims not to describe falsified medications in great detail, some issues should be briefly highlighted with examples. As with recalled and withdrawn drugs, falsified medicines pose a challenge for pharmaceutical policy and international cooperation, and all actions aimed to mitigate the risk for patients are highly warranted [19]. One of the leading causes of this phenomenon has been the lack of international legislation; however, recently introduced Falsified Medicines Directive (FMD) and acts enacted by Food and Drug Administration (FDA) has significantly improved the situation. One can hardly underestimate the role of the above-mentioned legal acts in the global fight against falsified and counterfeit medications. Corruption, the complexity of stakeholders involved in drug distribution, high market prices, and many other factors have impacted globalization of the phenomenon. Considering this problem, there is also important financial and humanistic burden. On the one hand, this practice is associated with high income for parties involved in this crime. On the other hand, it may lead to a poorer prognosis, disability and, in some dramatic scenarios, death [20]. Finally, patient safety remains at significant risk whenever even a single falsified drug is made available on the market. Beyond reasonable doubt, it can be assumed that constant improvement in drug quality along with close and transparent cooperation between stakeholders can not only minimize the risk of the occurrence of unwanted falsified drugs in legal distribution but can also lead to better allocation of finite drug supplies [21].

It can be admitted here that there is a little terminological discrepancy between falsified medications, which are deliberately falsified and introduced into the market as an imitation of non-falsified drugs, and those medications which are produced in violation of intellectual property rights. European legislation, particularly in the FMD, falsified medicines are accepted as the best way to describe deliberate misrepresentation. Borup et al. [22] have noticed that creating the legal framework in the pharmaceutical sector is a complex task requiring a multidimensional approach and harmonization of national legislation with European legal acts, which was clearly seen in the FMD. At least in Europe, this act had started a broad discussion on the quality of drugs dispensed in legal distribution. According to the prior-mentioned study, legal purposes for instance; harmonization of definition were more established in the current European pharmaceutical policy than public health issues [22]. Moreover, the rigid approach authorized by the European Commission may not adequately respond to local needs [23, 24].

Falsified medications in cardiovascular medicine

Since cardiovascular diseases are highly prevalent in the population, cardiovascular medications are widely used, and due to the chronic nature of

cardiovascular diseases, in most cases, it is long-term therapy, from the initial diagnosis to death [25, 26]. In 2005, falsified atorvastatin was identified in the legal distribution in the United Kingdom [27]. Clopidogrel, an antiplatelet agent, was also falsified in the United Kingdom. It should be noted that falsified stocks were obtained via parallel distribution, and traceability was highly impeded in this case. It was eventually revealed that formulation had not contained a sufficient amount of the active substance, which might have affected clinical efficacy [28, 29]. It is worth remembering. One cannot forget the heparin adulteration, which occurred in the United States in 2008. As a consequence of this affair, 81 people were killed, and almost 800 patients were severely harmed. They have been living and will live with long-standing health problems for the rest of their lives [30]. Good Manufacturing Practice violations were also identified in the heparin-related case of 2016. However, it did not have direct severe repercussions on patient health [31].

Substandard and falsified medications are a serious problem for developing countries. Antignac et al. [32] investigated the quality of cardiovascular drugs in 10 Sub-Saharan Countries (The Seven Study), and revealed that almost 20% of analyzed formulations had been classified to be of poor quality. The authors did not decide to conduct a forensic investigation and trace whether a particular formulation was falsified or was substandard, which should be considered a significant limitation. According to available research, this paper is a unique study; since there is a lack of research aimed at a particular class of drugs used in a specialized field of medicine, as was stated in the original paper. The fake amlodipine was also distributed in Kenya in 2014. Patients were officially informed about the potential risks related to the use of this falsified medication. Moreover, the differences between the original and fake packages were provided in official communications [33].

The plague of 'unwanted' drug recalls

Valsartan recall has been widely discussed in international media [34–36]. The formulations containing valsartan were recalled due to identified contamination with N-nitroso dimethylamine (NDMA), a potentially cancerogenic substance, resulting from unintended changes in the manufacturing process in China. Since contamination was related to an active pharmaceutical ingredient production, more than one brand had to be removed from the market.

Moreover, due to the chronic nature of both arterial hypertension and congestive heart failure — two of the most common indications for its use — valsartan is often prescribed for long-term therapy, which could potentially cause prolonged exposure to a cancerogenic substance, leading to substantial risk for developing malignancy [37, 38]. So far, studies have highlighted minimal short-term risk. Nevertheless, the real consequences should be a matter for further scientific and clinical discussion, also in terms of preventive screening among those exposed to the contamination over a long period [39, 40].

Cable News Network provided a list of recommendations to minimize the dissemination of false information among patients who used valsartan-containing products. The first piece of advice emphasized that some formulations, still available on the market at that moment, were safe for patients and did not contain hazardous contaminants. The media corporation also suggested that there were safe alternatives for patients, mostly in terms of drug equivalents, e.g., drugs belonging to a different therapeutic group with a similar hypotensive effect and toxicity profile, which can be a reasonable alternative for valsartan. The next part of the article described the association between exposure to contamination and cancer growth. Finally, the last piece of advice explained that using drugs should not be understood as a substitute for a good lifestyle, which is generally true, and applied not only to valsartan recall [41]. European Medicines Agency (EMA) urged national regulatory agencies to take appropriate steps to monitor drugs containing valsartan, specifically those produced in China. Nevertheless, in an official press release, EMA emphasized that all actions taken by authorities were precautionary, and actual risk to patients remained under control [42].

The contamination with NDMA is also a key reason behind the recall of formulations containing ranitidine. The FDA announced that, though unintended contamination was detected, the risk to patients was minimal since the level of NDMA barely exceeded concentration in food eaten on a daily basis by the vast majority of people around the world [43]. FDA, in a set of official public releases, revealed various aspects of valsartan and ranitidine recalls. FDA emphasized that an essential part of the recall was to educate patients about possible alternatives for ranitidine, and that patients should not stop their treatment unless they receive personalized recommendations from healthcare professionals [44]. It is important to note that

press releases were highly reassuring, brought the emotional level down, and emphasized the role of patient-oriented education as a tool for securing safety [45]. In addition, the FDA also revealed unwanted deviations from Good Manufacturing Practice, e.g., lack of adequate written procedures and problems with cleaning equipment used in drug production. Canadian authorities indicated that the problem with drugs containing ranitidine shared many similarities with a previously-described case with valsartan; however, since ranitidine is available over-the-counter, practical implications may have more serious consequences [46].

In light of all cases, the EMA recommended taking a proactive role and to extend the experience gained in valsartan and ranitidine-related cases to all medications. All actions should be aimed at reassuring patients that medicines are safe, effective, and without potentially cancerogenic ingredients, at least from a clinically relevant point of view. A different set of regulations should be given to clarify how to prevent future contamination with the NMDA [47].

The unwanted contamination of medicinal products containing valsartan and ranitidine had multiple repercussions in less developed countries as well. Safety alerts and drug recalls were introduced in Pakistan, where seven products with valsartan had been recalled from the market immediately after an official statement was authorized by American and European agencies had been published [48]. On the other hand, Moldova does not have well-prepared procedures regarding drug recalls, and the current situation there remains unclear [49].

Losartan and irbesartan were also investigated in terms of nitrosamine impurities [50]. As a result of this investigation, formulations containing losartan and losartan with hydrochlorothiazide were also recalled from the market; however, it should be noted that some products were recalled voluntarily by manufacturers just after the first signals from the market [51]. The same procedure was also implemented in the case of products containing irbesartan. In both above-mentioned cases, media attention was less prominent compared with the 'plague' of valsartan recalls [52, 53].

Summary

Falsified and substandard medications are an important threat to patient safety and public health. The occurrence of falsified medications in legal distribution has been making this situation even worse, particularly since over-the-counter medications are among the most frequently falsified categories of medications. The examples of falsified cardiovascular medications have confirmed that this phenomenon is, however, not only limited to non-prescription drugs. The second problem described in the paper herein, refers to drug recalls due to safety concerns. In recent years, many formulations used in cardiovascular medicine have been recalled from the market due to unwanted impurities or potentially carcinogenic substances. Both phenomena may have an impact on a patients' perspective on the safety and effectiveness of pharmacotherapy, potentially including hard outcomes. In this field, further studies are strongly recommended. Similar situations of a mass drug recall, as well as drug counterfeiting, should not take place. Authorities and parties involved in creating pharmaceutical policy should focus on ensuring patient safety, both from a legal and a societal point of view.

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IMPACT of PCSK9 inhibition on clinical outcome in patients during the inflammatory stage of the SARS-COV-2 infection: Rationale and protocol of the IMPACT-SIRIO 5 study

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Introduction

Coronavirus disease 2019 (COVID-19) infection is characterized by distinct stages: the first one with dominant replication of the virus, and the second one with dominant immunological inflammatory response of the host [1]. COVID-19 can evolve into a systemic severe inflammatory response characterized by cytokine storm and acute respiratory distress syndrome. Cytokine storm refers to a set of clinical conditions caused by excessive immune reactions and has been recognized as a leading cause of severe COVID-19, multiple organ dysfunction syndrome and adverse clinical outcomes [2–6]. Various laboratory markers have been linked with COVID-19-related excessive inflammatory response caused by cytokine release syndrome. Among cytokines, interleukin (IL)-6, IL-8, and tumor necrosis factor alpha (TNF-α) are regarded as the most relevant triggers of the hyperinflammatory reaction during COVID-19 [7–9]. Furthermore, microvascular and macrovascular thrombosis are observed complications in COVID-19 which in turn may be the target of therapeutic strategies to significant influence disease-related sequelae and mortality [5–7].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that plays a crucial role in the homeostasis of low-density lipoprotein (LDL) receptors (LDLR), however, it also promotes inflammatory response [10]. Experimental and clinical data suggest that in addition to improvement in lipid profile and clinical outcomes in patients with cardiovascular diseases, PCSK9 inhibitors also exert an anti-inflammatory effect that might be related to interference on the IL-6 pathway [10–15].

Herein, is a discussion of the rationale for the use of PCSK9 inhibitors in the treatment during the hyperinflammatory stage of COVID-19 and present a design of the ongoing study in testing this hypothesis (NCT04941105).

PCSK9 and inflammation/thrombosis

PCSK9 is a protein that is expressed in the liver, intestine, and kidneys, while circulating PCSK9 originates exclusively from hepatocytes [16, 17]. The physiological role of PCSK9 is to

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mediate the LDLR degradation and thus to regulate the LDL cholesterol (LDL-C) homeostasis [18]. Moreover, PCSK9 has also been shown to have a pro-inflammatory effect [12, 19, 20]. Overexpression of PCSK9 in macrophages increases the expression of IL-1β and TNF-α, and decreases the anti-inflammatory markers Arg1 and IL-10 [21]. PCSK9 can act as trigger of inflammatory response as it causes increased expression of Lectin-like oxidized LDL receptor-1 (LOX-1) enhancing oxidized LDL (ox-LDL) uptake and amplifying the inflammatory response [10]. This pivotal interaction links cholesterol accumulation and chronic inflammatory process of atherosclerosis. Further data suggest that the nuclear factor kappa B (NF-κB) signaling pathway plays a key role in PCSK9-mediated vascular inflammation and thrombosis [20–22]. In fact, PCSK9 inhibition by using small interfering RNA (siRNA) has shown to suppress expression of LOX-1 and secretion of pro-inflammatory cytokines in macrophages by inhibiting NF-κB translocation into the nucleus [22–26].

PCSK9 during infection

Experimental data have shown that that heightened inflammation mediated by IL-6, may represent the biochemical link between HIV/HCV coinfection and elevated PCSK9 levels. This relationship may be bidirectional (PCSK9 regulating levels of IL-6) because healthy individuals with PCSK9 loss of function mutations have less IL-6 in response to lipopolysaccharide-induced inflammation [7, 27]. Dwivedi et al. [14] found that overexpression of PCSK9 was associated with increased liver and kidney pathology, plasma IL-6, alanine aminotransferase, and thrombin–antithrombin complexes concentrations during sepsis, whereas PCSK9 knockout mice exhibited reduced bacterial loads, lung and liver pathology, myeloperoxidase activity, plasma IL-10, and cell-free DNA (a procoagulant molecule released mainly by activated neutrophils) in a murine model of sepsis. Moreover, dyspnea, cyanosis, and overall grimace scores (severity of pain assessment) were higher in septic mice overexpressing PCSK9. Furthermore, lower expression of inflammation in PCSK9 knockout mice was confirmed by retained core body temperature during sepsis [14]. Results of this comprehensive experiment strongly suggest the strong impact of PCSK9 expression also on systemic, but not only local, inflammation and coagulation. These observations were in line with other data [27], which demonstrated that human PCSK9 loss-of-function genetic variants were associated with improved survival in septic shock patients and a decrease in systemic inflammatory cytokine response both in septic shock patients and in healthy volunteers after lipopolysaccharides (pathogenic lipid moieties from Gram-negative bacteria cell walls) administration. Moreover, a positive correlation between plasma levels of PCSK9 and TNF-α, in a population of overall healthy subjects further supports the impact of PCSK9 on the systemic inflammatory response [28].

PCSK9 inhibition and inflammation

PCSK9 inhibition is associated with reduced monocyte recruitment and attenuated ox-LDL--induced expression of pro-inflammatory chemokine synthesis and secretion. Anti-PCSK9 antibodies alirocumab and evolocumab have been shown to decrease LDL-C level and reduce cardiovascular events in multiple clinical studies [29–36]. An experimental study in a mice model confirmed cholesterol lowering effect of PCSK9 inhibition and atherosclerosis development prevention also shows a reduction of inflammatory markers in mononuclear cells (IL-6, TNF-α mRNA) and in serum (CXCL-1, -10, -13, complement factor C5a) [16]. Furthermore, reduction of macrophage plaque infiltration and inflammation was found. These effects were associated with increased number of circulating endothelial progenitor cells and circulating angiogenic cells that are considered markers of endothelial and vascular health and are associated with positive clinical outcomes [15]. Additionally, reduced PCSK9 function is associated with increased pathogen lipid clearance via the LDLR, a decreased inflammatory response, and improved outcome in septic shock [27].

Interleukin-6 in COVID-19 cytokine storm

Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been classified into three clinical stages, regarding the severity and prognosis. Stage I is defined by mild unspecified symptoms of infection, such as myalgia, dry cough, headache, and subfebrile temperature, without any laboratory and radiological abnormalities. Stage II is characterized by cough, high fever, dyspnea, abnormal thoracic imaging, lymphopenia, and increased levels of inflammatory markers. This stage is further divided according to the presence (IIb) or absence (IIa) of hypoxemia. Stage III dis-

plays clinical manifestations of a severe systemic inflammatory syndrome, culminating in severe respiratory failure with an unfavorable prognosis [37, 38]. The increased levels of a large array of pro-inflammatory cytokines has been recognized as crucial in the pathophysiology of severe COVID-19 [8, 39].

Hyper-inflammatory response, also referred to as "cytokine storm" is an immune dysregulation which can lead to multiorgan failure and death through systemic inflammation. Various therapies, pathogens, cancers, autoimmune conditions, and monogenic disorders can trigger the immune hyperactivation related to unrestrained cytokine release [40]. Generally, the cytokine pattern depends on the underlying cause. The list of potential symptoms of cytokine storm significantly overlap with symptoms of COVID-19, and include high grade fever, fatigue, cough, headache, diarrhea, arthralgia, myalgia, disseminated intravascular coagulation dyspnea, hypoxemia, hypotension, vasodilatory shock, acute respiratory distress syndrome and multiple organ dysfunction syndrome [40, 41].

Cytokine storm with excessive release of inflammatory mediators induced by SARS-CoV-2 is a major cause of disease severity and death. In recent studies conducted in adults with polymerase chain reaction-proven SARS-CoV-2 infection IL-6 level was shown predict death better than age or C-reactive protein (CRP). Moreover, the kinetic quantification of IL-6 levels allowed early discrimination between survivors and non-survivors [42]. These findings were in line with several other studies showing its good correlation to disease severity, the risk of needing mechanical ventilation, or death [43–47]. IL-6 has also been shown to be a prognostic marker of clinical worsening within 1–2 days from stage IIb to stage III. This pattern was not observed for CRP levels, despite the positive correlation between IL-6 and CRP [42]. Hadjadj et al. [48] showed that IL-6 was not detected in peripheral blood at the transcriptional level, contrasting with high amounts of IL-6 protein during the inflammatory response in COVID-19. Expression of IL-6-induced genes (IL6R, SOCS3, and STAT3) was significantly increased, reflecting the activation of the IL-6 signaling pathway. TNF-α was only moderately up-regulated at the transcriptional level, whereas circulating TNF-α was significantly increased. Accordingly, TNF pathway–related genes were also up-regulated, including TNFSF10, which supports TNF-α having an important role in the induction of inflammation [43, 44, 48]. Inflammatory markers decline in patients who clinically improve (transition from phase IIb to IIa) and increase in those who experience worsening (transition from phase IIb to III). The critical inflammation point based on IL-6 monitoring of the disease seems to occur around 1 week to 10 days after the onset of symptoms [42]. This is in line with clinical observations in severe COVID-19 cases typically showing a two-step disease progression, starting with a mild-to-moderate presentation followed by a secondary respiratory worsening 9 to 12 days after the first onset of symptoms. This biphasic evolution marked by a substantial increase of acute phase reactants in the blood suggests a dysregulated inflammatory host response, resulting in an imbalance between pro- and anti-inflammatory mediators [48].

Therefore, it was hypothesized that there is a narrow period of time in which immunomodulatory drugs may be particularly effective and that therapeutics guided by the IL-6 level, in which randomization would occur only in patients with levels of IL-6 above a certain cut-off, could guide new therapeutic strategies and further improve outcomes [42].

Interleukin-6 repetitively emerges in subsequent reports from studies evaluating excessive cytokine release in patients with COVID-19 indicating a crucial role this cytokine plays in the pathophysiology of the disease. Many different cell types, e.g. monocytes, macrophages, fibroblasts, keratinocytes, astrocytes, endothelial cells, activated B cells and T cells, can secrete IL-6 upon appropriate stimulation [49, 50]. The main roles of IL-6 include regulation of cell responses of B and T cells and coordinates the activity of the innate and the adaptive immune systems [50].

Clinical efficacy of selective inhibition of IL-6 in COVID-19

Due to its central role in the cytokine storm during COVID-19, IL-6 signaling has been targeted as one of the most promising directions in the treatment of excessive inflammatory response in patients with SARS-CoV-2 infection [51]. Out of several anti-IL-6 pathway substances that are approved in various indications (Table 1), baricitinib, sarilumab and tocilizumab were evaluated in COVID-19.

The largest randomized clinical trial evaluating barcitinib, a Janus kinase (JAK) inhibitor, in a treatment of COVID-19 included 1033 patients. Barcitinib used together with remdesivir led to shorter time to recovery (7 vs. 8 days) and acceler-

Table 1. Approved drugs that target interleukin-6 signaling.

Compound	Target	Medical conditions
Baricitinib	JAK-1, JAK-2	Rheumatoid arthritis, atopic dermatitis
Filgotinib	JAK-1	Rheumatoid arthritis
Ruxolitinib	JAK-1, JAK-2	Myelofibrosis, polycythaemia vera
Sarilumab	IL-6R	Rheumatoid arthritis
Siltuximab	IL-6	Castleman disease
Tocilizumab	IL-6R	Rheumatoid arthritis, juvenile idiopathic arthritis, Castleman disease, giant cell arteritis, cytokine release syndrome
Tofacitinib	JAK-1, JAK-2, JAK-3	Rheumatoid arthritis, Psoriatic arthritis, ulcerative colitis
Upadacitinib	JAK-1	Rheumatoid arthritis

ated improvement in clinical status (10 vs. 18 days) compared with patients receiving remdesivir alone. The 28-day mortality was numerically lower in the combined treatment group, but without reaching the statistical significance (5.1% vs. 7.8%, hazard ratio [HR] 0.65; 95% confidence interval [CI] 0.39––1.09) [52]. Meta-analyses of the efficacy of JAK inhibitors in COVID-19 suggest their impact on the reduced risk of mortality (odds ratio [OR] 0.51, 95% CI 0.28–0.93, p = 0.02), with higher relative risk reduction observed with barcitinib compared with ruxolitinib, as well as clinical improvement (OR 1.76, 95% CI 1.05–2.95, p = 0.032) [53, 54]. The main limitation of available data on barcitinib in COVID-19 is a lack of large, uniformly reported randomized studies.

Sarilumab is a monoclonal antibody that targets the IL-6 receptor (IL-6R). In a study by Lescure et al. [55] sarilumab compared with placebo did not reduce time to improvement or survival rate at 28 days in hospitalized patients with SARS-CoV-2 infection who required supplemental oxygen. On the other hand, in the REMAP-CAP study blockade of IL-6R by sarilumab or tocilizumab compared with placebo resulted in improved in-hospital survival in critically ill COVID-19 patients (78%, 72%, and 64%, respectively) [56]. However, clinical application of these results remains limited due to the fact that the sarilumab arm included only 48 patients.

Much more data is available on the use of tocilizumab for the treatment of patients with SARS-CoV-2 infection. Numerous trials with this IL-6R antagonist have been conducted so far, and meta-analyses of these heterogeneous studies indicate that use of tocilizumab is associated with decreased risk of death, but does not demonstrate benefits for surrogate endpoints including intensive care unit admission, invasive mechanical ventilation or secondary infections [57, 58].

PCSK9 and thrombosis

COVID-19 patients are at heightened risk of thrombosis [2–5]. PCSK9 might be implicated in the increased thrombotic risk during the more advanced stages of COVID-19.

Several mechanisms support this hypothesis. A recent investigation found that PCSK9 directly causes platelet aggregation by activating the CD36 downstream signalling pathways [14]. Increased plasma PCSK9 levels lead to elevated LDL and, subsequently, ox-LDL levels. The ox-LDL binds to the lecithin-like ox-LDL receptor (LOX-1) and CD36 on platelets and activates cytosolic phospholipase A2 (cPLA2). CD36 binds various ligands, leading to different effects. In particular, cPLA2 releases arachidonic acid from membrane phospholipids that is subsequently converted to thromboxane (Tx) A2 by cyclooxygenase (COX)-1/ /thromboxane synthase activity. TxA2 acts synergistically with downstream signalling generated by the binding of platelet agonists (adenosine diphosphate, collagen, and thrombin) to respective receptors to activate glycoprotein (GP) IIb/IIIa receptors. Activated GP IIb/IIIa receptors from adjacent platelets bind to fibrinogen forming platelet aggregation [23]. Increased plasma PCSK9 is associated with increased platelet activation in acute coronary syndrome [35].

Experimental data in the CD36-knockout mice model demonstrated that enhancing effects of PCSK9 on platelet activation are mediated by a direct binding on CD36 platelet surface and abolished by administration of PCSK9i or acetylsalicylic acid [14]. Notably, in the animal model of myocardial infarction, PCSK9-dependent platelet activation triggered microvascular obstruction and promoted the expansion of the infarction, possibly through increased oxidative stress, PCSK9 also modulates

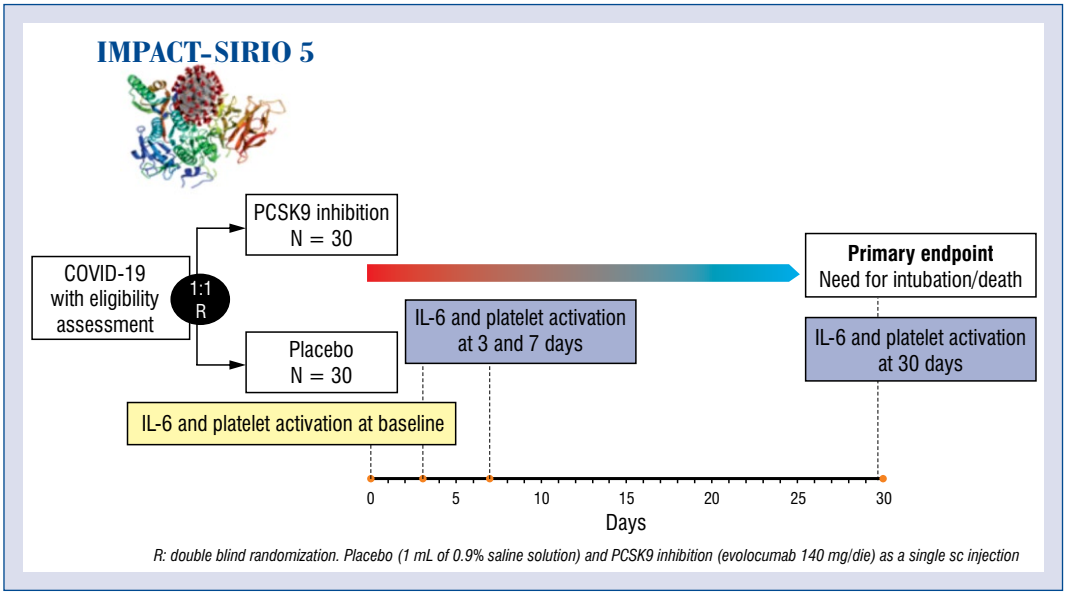

Figure 1. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition on clinical outcome in patients; COVID-19 — coronavirus disease 19; IL-6 — interleukin 6.

thrombosis by modifying platelet steady-state, leukocyte recruitment and clot formation [59]. In particular, platelets from PCSK9 knockout mice showed a significant reduction of glycoprotein IIb/IIIa and P-selectin expression, as well as of circulating platelet-leukocyte aggregates compared to wild type mice, indicating a lower platelet activation in the former [60].

Methods

Despite the progress in vaccination campaigns against SARS-CoV-2, the number of new variants and active infections continues to grow [61].

PCSK9 inhibition may represent a novel therapeutic pathway in COVID-19 which can act on top of those previously included into standard therapeutic approaches in COVID-19. The present study was designed to evaluate the impact of PCSK9 inhibition on clinical outcome in patients during the inflammatory stage of the SARS-CoV-2 infection.

This is a phase III, multicenter, double-blind, randomized, investigator-initiated clinical trial evaluating the efficacy and safety of PCSK9 inhibitors in the treatment of SARS-CoV-2 infected patients with cytokine storm stage. Patients will be randomized in 1:1 ratio into one of two study arms: treatment group and control group. Patients assigned to the treatment group will receive a PCSK9 inhibitor evolocumab. Patients in the control group will receive an injection of 1 mL of 0.9% NaCl. In addition, all people included in the study will be treated in accordance with the current therapeutic recommendations for COVID-19 patients. All study participants will be followed up for 30 days. In addition, a safety follow-up extended to 1 year is planned with an additional evaluation of functioning in disease with the Functioning in Chronic Diseases Scale (FCIS) [62–65]. The primary endpoints are the need for intubation and all-cause death.

As there are no previous data to determine the number of subjects to be enrolled into the study for adequate power we have started a pilot study: Impact of PCSK9 inhibition on clinical outcome in patients during the inflammatory stage of the COVID-19 (IMPACT-SIRIO 5); ClinicalTrials.gov Identifier: NCT04941105. It was designed as the randomized, double-blind, multicenter, phase III study with a 30-day follow-up. The study was approved on October 27, 2020 by The Ethics Committee of Nicolaus Copernicus University in Torun, Collegium Medicum in Bydgoszcz (study approval reference number KB468/2020).

The plan is to enroll 60 consecutive patients in a 1:1 ratio to the experimental and control arm. In the experimental arm 140 mg of evolocumab as a single subcutaneous injection is administered, while in the control arm 1 mL of 0.9% saline solution given as a single subcutaneous injection serves as a comparator. All patients are treated in accordance to the latest recommendations on caring for patients infected with SARS-CoV-2 (Fig. 1).

Primary outcome measures

1. Need for intubation (the indications for intubation determined individually for each patient and clinical status)
2. Death from any cause

Primary laboratory endpoint

1. Change in serum IL-6 concentration from day 0 to day 3
2. Change in serum IL-6 concentration from day 0 to day 7

Secondary outcome measures

1. The time of invasive mechanical ventilation
2. The time with non-invasive mechanical ventilation or high-flow nasal cannula
3. The time with oxygen therapy
4. The duration of hospitalization
5. Discontinuation of oxygen therapy before discharge

Inclusion criteria

1. Written informed consent for participation in the study
2. Male and female age ≥ 18 at the time of signing the informed consent
3. SARS-CoV-2 infection confirmed by real-time reverse transcription polymerase chain reaction
4. COVID-19 pneumonia with typical radiological changes
5. PaO_2/FIO_2 ratio ≤ 300
6. COVID-19 cytokine storm with elevated serum level of IL-6 > 25 pg/mL

Exclusion criteria

1. Use of fibrates other than fenofibrate or fenofibric acid
2. Known active infections or other clinical condition that contraindicate PCSK9 inhibitors
3. Known systemic hypersensitivity to PCSK9 inhibitors
4. Estimated glomerular filtration rate < 30 mL/min/1.73 m^2
5. Absolute neutrophil count < 2000/mm^3
6. A platelet count < 50000/mm^3
7. Creatine kinase greater than 3× upper limit of normal
8. Aspartate aminotransferase or alanine aminotransferase greater than 3× upper limit of normal
9. Not expected to survive for > 48 hours from screening
10. Unrelated co-morbidity with life expectancy < 3 months
11. Pregnancy
12. Any physical examination findings and/or history of any illness that, in the opinion of the study investigator, might confound the results of the study or pose an additional risk to the patient by their participation in the study
13. Patient being treated with other immunomodulators (except for glucocorticoids)
14. Patient included in any other interventional trial

Discussion

Summing up, strong scientific evidence exists that PCSK9 promotes the systemic inflammatory response. On the other hand, PCSK9 inhibition has been shown to reduce IL-6 mediated inflammation pathway in experimental studies. Hyperinflammatory response, also called a "cytokine storm" with excessive release of inflammatory mediators induced by SARS-CoV-2 is a major cause of COVID-19 severity and death. IL-6 has been shown to be the best prognostic marker of clinical deterioration and mortality in patients developing cytokine storm. It was hypothesized that there is a narrow time window in which IL-6-guided immunomodulatory therapy may be particularly effective. The preliminary experience with anti-IL-6 pathway substances application in COVID-19 is promising. Moreover, according to available data, therapy with PCSK9 inhibitors is expected to reduce the rate of thrombotic complications due to the antiplatelet effect.

Conflict of interest: None declared

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Low-dose ticagrelor with or without acetylsalicylic acid in patients with acute coronary syndrome: Rationale and design of the ELECTRA-SIRIO 2 trial

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Introduction

In patients with acute coronary syndrome (ACS), dual antiplatelet therapy (DAPT) with ticagrelor 90 mg twice daily (b.i.d.) on top of acetylsalicylic acid (ASA) is recommended for 12 months to reduce adverse thrombotic events. In subjects at high ischemic risk who have tolerated DAPT without a bleeding complication, continuation of ticagrelor 60 mg b.i.d. for longer than 12 months may be considered [1].

Increased ischemic risk occurs in the early period after ACS, with elevated rates of clinical events clustering during the first month, which is reflective of elevated platelet reactivity [2]. On the other hand, bleeding risk increases in a stepwise fashion after cumulative administration of an antiplatelet agent. It is related to the duration and dose of the antiplatelet treatment, and the majority of bleeding events occur after 30 days following ACS [2]. This means that the ischemic component should be targeted with potent antiplatelet strategies in the earliest phase after ACS, whereas de-escalation of the antiplatelet therapy could be justified after clinical stabilization occurs.

Pharmacodynamic data show that a reduction of ticagrelor bioavailability by ~30% significantly decreases its antiplatelet effect in patients with acute myocardial infarction (MI), but not in stable subjects with prior MI [3, 4]. Still, in patients > 1 year after MI the equivalent pharmacodynamic effects of ticagrelor 90 mg b.i.d. and 60 mg b.i.d. provide comparable clinical efficacy, with a better tolerability of treatment observed with a lower dose [3, 5]. Recently, it was demonstrated that ticagrelor 60 mg b.i.d. also provides a similar antiplatelet effect to 90 mg b.i.d. already 1 month after MI [6].

In the TWILIGHT study, high-risk patients who had undergone percutaneous coronary intervention (PCI) and were treated with ticagrelor 90 mg b.i.d. monotherapy following 3 months of standard DAPT, experienced fewer bleeding events than patients receiving ticagrelor with ASA, without ischemic harm over a period of 1 year [7].

It was hypothesized herein, that the reduction of ticagrelor maintenance dose to 60 mg b.i.d. 1 month after ACS, followed by ASA withdrawal at 3 months after ACS will result in improved safety and tolerability of treatment with preserved anti-ischemic benefit [8]. The aim of the Evaluation of safety and efficacy of two ticagrelor-based de-escalation antiplatelet strategies in acute coronary syndrome — a randomized clinical trial (ELECTRA-SIRIO 2) is to assess the influence of early ticagrelor dose reduction with or without discontinuation of ASA on clinically relevant bleeding and maintenance of anti-ischemic efficacy after ACS.

Methods

Study design and population

The ELECTRA-SIRIO 2 study is a phase III, randomized, multicenter, double-blind, investigator-initiated clinical trial with a 12 month follow-up. The study population will include 4500 patients admitted to the study centers due to ACS, including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI) and unstable angina (UA). The diagnosis of STEMI and NSTEMI will be made according to the Fourth Universal Definition of Myocardial Infarction [9], and UA will be diagnosed according to the 2020 European Society of Cardiology (ESC) guidelines for the management of non-ST-segment elevation ACS (NSTE-ACS) [10]. STEMI patients will have to be qualified for the primary PCI to be eligible for the inclusion. To be enrolled into the study, patients with NSTE-ACS (NSTEMI or UA) will have to fulfill at least one of the following criteria: 1) ≥ 60 years old; 2) previous MI or coronary artery by-pass grafting; 3) ≥ 50% stenosis in ≥ 2 coronary arteries; 4) previous ischemic stroke or transient ischaemic attack; 5) ≥ 50% carotid stenosis or cerebral revascularization; 6) diabetes mellitus; 7) peripheral artery disease; 8) chronic kidney disease with glomerular filtration rate (GFR) < 60 mL/min. The exclusion criteria include, among others, indications for oral anticoagulation therapy and end stage kidney disease with GFR < 15 mL/min or on dialysis. **Supplementary Appendix** contains the complete list of inclusion and exclusion criteria.

All participants will receive loading doses of 180 mg ticagrelor and 300 mg ASA. Patients loaded with clopidogrel before the study inclusion will be re-loaded with 180 mg ticagrelor upon enrolment. Participants will be randomized in a 1:1:1 ratio into the following arms: low-dose ticagrelor with ASA (LDTA), low-dose ticagrelor with placebo (LDTP), and standard-dose ticagrelor with ASA (SDTA), the latter being the control arm. During the first month after ACS patients from all three groups will receive a standard DAPT with ticagrelor 90 mg b.i.d and 100 mg ASA once daily. Patients assigned to the control group (SDTA) will continue this treatment for 12 months. Patients allocated to the experimental arms (LDTA and LDTP) will receive reduced maintenance dose of ticagrelor

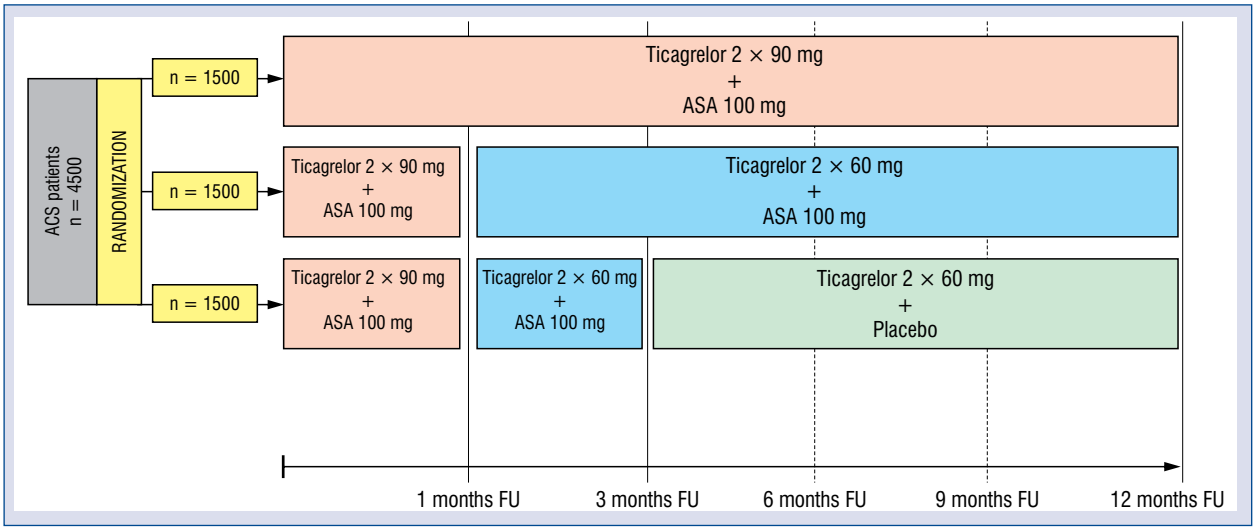

Figure 1. Design of the trial; ASA — acetylsalicylic acid; ACS — acute coronary syndrome; FU — follow-up.

60 mg b.i.d. and 100 mg ASA q.d starting after the first month following ACS. Patients from the LDTA arm will continue this treatment until 12 months after ACS, while patients from the LDTP arm will additionally discontinue ASA 3 months after ACS and continue on ticagrelor 60 mg b.i.d. monotherapy until 12 months after ACS. All participants are expected to undergo 5 out-patient follow-up visits as depicted in Figure 1.

All study participants will be provided with blinded packages containing the antiplatelet medications (ticagrelor 60 mg or 90 mg, and ASA 100 mg or placebo) according to the randomized allocation. The dispended medications will be free of charge and will be sufficient to cover the whole period (12 months) of each patient in the study.

Each patient will provide written informed consent to participate in the study. The study will be conducted in accordance with the Good Clinical Practice guidelines and with the regulations contained in the Declaration of Helsinki. The trial was approved by the appropriate Ethics Committee to conduct the study (study approval reference number KB 379/2020). ClinicalTrials.gov Identifier: NCT04718025.

Treatment protocol and concomitant medications

Apart from the investigated strategies, enrolled patients will be treated according to the current ESC guidelines, however cholesterol-lowering treatment with high doses of statins will only be allowed (≥ 40 mg atorvastatin or ≥ 20 mg rosuvastatin), unless contraindicated, and the addition of ezetimibe will be recommended. Use of stents with ultra-thin or thin struts will be highly recommended during PCI in order to decrease the thrombotic risk related to stent implantation [11].

Study endpoints

The primary safety composite endpoint is the first occurrence of type 2, 3 or 5 bleeding according to the Bleeding Academic Research Consortium (BARC) criteria. The primary efficacy endpoint is the composite of time to death from any cause, first nonfatal MI, or first nonfatal stroke. The key secondary endpoint, net clinical effect, was defined as composite of death from any cause, nonfatal MI, or nonfatal stroke, and the first occurrence of BARC type 2, 3, or 5 bleeding. Remaining secondary endpoints include: death from any cause, cardiovascular death, MI, ischemic stroke, definite or probable stent thrombosis, dyspnea, BARC type 3 or 5 bleeding, Thrombolysis in Myocardial Infarction (TIMI) major or minor bleeding, Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) moderate or severe or life-threatening bleeding, International Society on Thrombosis and Hemostasis (ISTH) major bleeding.

Sub-group analyses

Prespecified subanalyses will be performed according to: 1) diabetes mellitus; 2) chronic kidney disease (GFR < 60 mL/min/1.73 m^2); 3) gender; 4) age; 5) type of ACS; 6) administration of morphine during the index event; 7) presence or absence of multivessel disease. Additionally, impact of the following characteristics on the clinical outcomes will be evaluated: 1) complexity of coronary revas-

cularization; 2) lipid-lowering treatment; 3) results in the MEDMOTION project (**Suppl. Appendix**).

Safety monitoring

The trial will be overseen by the international Steering Committee, clinical events committee, and data and safety monitoring board (DSMB). The safety of the tested antiplatelet strategies, all clinical events, and any deviations to the study protocol will be periodically monitored based on electronic medical documentation by an independent DSMB. Based on the safety data, the DSMB may recommend modifications to the protocol, suspension or termination of the study. All final decisions regarding trial modifications rest with the Steering Committee.

Statistical analysis

Sample size and power calculation were based on a superiority assumption for the primary safety endpoint for LDTP vs. SDTA arm. Assuming a bleeding incidence of 7.1% at 1 year with standard dose ticagrelor plus ASA (rate reported in the TWILIGHT study [7]), a sample size of 1178 patients per arm is required to provide 95% power to detect 40% lower incidence of the primary safety composite endpoint in LDTP vs. SDTA group (43.6% relative reduction observed in ticagrelor monotherapy arm of the TWILIGHT trial), with a type I error rate of 0.05.

The primary efficacy endpoint (composite of death from any cause, nonfatal MI, or nonfatal stroke) will be evaluated with the use of a prespecified noninferiority hypothesis (LDTP vs. SDTA). Under the assumption of an incidence of 10.2% (occurrence rate reported for this endpoint in the PLATO study at 1 year in the SDTA, a sample size of 1204 patients per arm is needed to provide 90% power to rule out an absolute difference in risk of 1.6 percentage points, with a one-sided type I error rate of 0.025 (assumption made for the sample size calculations made in the TWILIGHT study).

Enrolment of a total of 4500 patients (1500 in each arm) is planned to compensate the potential drop-out from the study up to 20%. This broad margin has been chosen as the time between randomization and actual onset of the investigated strategies is 1 and 3 months for experimental LDTA and LDTP strategies, respectively, which may increase the risk of drop-out before the beginning of the allocated regimen.

Discussion

The primary hypothesis of the ELECTRA--SIRIO 2 study is that monotherapy with low-dose ticagrelor in ACS patients will lead to a significant reduction of clinically relevant bleeding compared with standard-dose ticagrelor with ASA. The additional study arm including DAPT with low-dose ticagrelor is intended to differentiate the impact of decreasing the ticagrelor dosage versus eliminating ASA from the antiplatelet treatment.

During the first month after ACS, increased platelet reactivity goes in pair with increased rate of adverse ischemic events. Therefore, DAPT with ticagrelor 90 mg b.i.d. is necessary to obtain adequate platelet inhibition and prevent thrombotic events during the initial phase of ACS treatment. Occurrence of thrombotic complications decreases over time, and reaches a stable level approximately 1 month after ACS which is related to reduced baseline platelet activation and potentially may allow treatment de-escalation [2].

A sub-study of the PEGASUS-TIMI 54 trial showed that in stable patients > 1 year after MI, ticagrelor 60 mg b.i.d. provides similar platelet inhibition as 90 mg b.i.d., explaining comparable clinical efficacy of both doses in this setting [3, 5]. Recently, it was reported that the same pharmacodynamic effects of low-dose vs. standard-dose ticagrelor already after 1 month following ACS. In the ELECTRA pilot study, there were no differences between the two regimens with regard to on-ticagrelor platelet inhibition, and the number of patients with optimal platelet reactivity was identical between the arms [6].

On the other hand, antiplatelet treatment is burdened with non-negligible side effects, greatly related to bleeding, that often may require medical attention or lead to discontinuation of treatment (e.g., rate of premature discontinuation of antiplatelet treatment in the PLATO study was 22–23%) [2]. Premature discontinuation of antiplatelet therapy, especially in invasively-treated patients, may lead to detrimental cardiovascular and thrombotic events, such as recurrent ACS or stent thrombosis. Several strategies aiming to enhance safety of antiplatelet treatment, without reducing its efficacy, have been evaluated so far.

Platelet function testing-guided de-escalation from prasugrel to clopidogrel was shown to be non-inferior to standard treatment with prasugrel at 1 year after PCI in terms of net clinical benefit. However, with this approach 39% of patients required a switch-back to prasugrel due to commonly observed insufficient platelet inhibition [12]. In another study, DAPT downgrading from prasugrel/ticagrelor to clopidogrel 1 month after ACS was associated with a net clinical benefit

driven by a reduction in bleeding complications, with unchanged risk of recurrent ischemic events [13]. Nonetheless, the SCOPE registry reported switching from novel P2Y12 receptor inhibitors to clopidogrel as an independent predictor of net adverse cerebrovascular events [14].

An interesting approach to decrease bleeding complications was evaluated in the TWILIGHT study. This trial has shown that switching from DAPT with ticagrelor 90 mg b.i.d. and ASA to ticagrelor 90 mg b.i.d. monotherapy at 3 months after ACS leads to a significant reduction in bleeding, with maintained antithrombotic effectiveness [7].

The antiplatelet de-escalation strategies proposed in the current trial (LDTA and LDTP) are expected to essentially decrease the incidence of clinically significant bleeding events during the first year after ACS without increasing the rates of thrombotic events. In contrast to the platelet function testing-guided de-escalation strategies, the concept proposed in the ELECTRA-SIRIO 2 study does not require platelet reactivity assessment, making this step-down approach more feasible for wide application in clinical practice [8]. Discontinuation of ASA, as investigated in the TWILIGHT study, resulted in reduction in clinically relevant bleeding episodes, including fatal bleeds, by 43% [7]. It can be assumed that lowering the daily dose of ticagrelor may only further decrease the rate of bleeding episodes.

Additionally, due to the expected dose-dependent reduction in therapy-related adverse effects, including dyspnea or bradycardia, an improved adherence to the treatment may be anticipated. In the PEGASUS-TIMI 54 trial dyspnea occurred less frequently in patients who received the lower dose of ticagrelor compared with those treated with the standard dose (16% vs. 19%) [5]. This also might be of importance as early termination of ticagrelor leaves ACS patients unprotected against ischemic consequences.

The TWILIGHT trial proved that monotherapy with a standard ticagrelor dose in high-risk stable patients is safer, but still equally effective, compared with ticagrelor-based DAPT. On the other hand, the ELECTRA pilot study showed the same level of platelet inhibition with standard and reduced ticagrelor doses in stable patients already 1 month after PCI for ACS [6]. To date, de-escalation of antiplatelet therapy in ACS patients based on decreasing the dose of ticagrelor with or without discontinuation of ASA has never been tested in a large randomized clinical trial. The design of the ELECTRA-SIRIO 2 trial includes both these strategies aiming to document reduction of clinically relevant bleeding, without compromising clinical efficacy in terms of prevention of adverse cardiovascular events.

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TECHNOLOGY NOTE

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Nicotinamide adenine dinucleotide fluorescence to assess microvascular disturbances in post-COVID-19 patients

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Coronavirus disease 2019 (COVID-19) revealed many different faces, from severe to completely asymptomatic course. An increasing number of patients are starting to emerge with significant cardiovascular problems, including myocarditis, heart failure, severe arrhythmias, and thromboembolic complications. Accumulating data suggest that COVID-19 is a systemic vascular endothelial dysfunction with different and unpredictable clinical manifestations, including pulmonary, neurological, cardiac, or thromboembolic problems. Of note, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) enters target cells via angiotensin-converting enzyme 2 (ACE2) receptors, which are widely expressed on the endothelial cells in several organs, including the heart and lungs [1]. Indeed, an increasing amount of evidence indicates that SARS-CoV-2 affects endothelial function via inflammation of endothelial cells (endotheliitis), causing microvascular disturbances and microthrombosis in different vascular beds, leading to COVID-19-related acute and long-term complications [2].

More precisely, SARS-CoV-2 affects vascular endothelium by multiple mechanisms, including a cytokine storm. Interestingly, exocytosis of granules from endothelial cells induces platelet aggregation and leukocyte influx into the vessel wall, which causes inflammation, microthrombosis, and capillary obstruction [3]. The blood flow disturbances in capillaries due to endotheliitis or accumulation of leukocytes shortens the time of blood flow resulting in reduced oxygen exchange between blood and tissue. Hypoxia of endothelial cells via transit-time effects leads to the further secretion of inflammatory cytokines, which provides another brick for endothelial damage [4].

Microcirculation plays a pivotal role in tissue oxygenation and nutrient supply. The decrease in oxygen delivery during endotheliitis may induce tissue hypoxia and inhibits metabolism. Accumulating evidence suggests that COVID-19-induced endotheliitis is predominately a systemic small-vessel vasculitis not involving the large arteries such as the main coronaries [5]. Owing to its accessibility, a peripheral microvascular function has been considered an indicator of general microvascular function [6]. Several methods are available to study peripheral microcirculation and attempt to quantify perfusion or oxygenation. However, we can currently assess the variation in tissue biochemistry in vivo using the measurements of a nicotinamide adenine dinucleotide (NADH) fluorescence signal intensity [7].

The newly developed flow-mediated skin fluorescence (FMSF) is a non-invasive optical technique to study microcirculation and metabolic regulation based on cutaneous NADH fluorescence intensity registration. Excitation of the forearm with ultraviolet light at 340 nm results in the emission of a NADH fluorescence signal from human epidermal cells. Indeed, the epidermis is particularly sensitive to hypoxia. The level of NADH fluorescence corresponds to the balance of mitochondrial oxidation-reduction processes occurring in the tissue, reflected by the balance between the oxidized form of the coenzyme (NAD^+)

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and its reduced form (NADH). The emitted fluorescence light of NADH at 460 nm is detected by the receiver diode and corresponds to the activity of microcirculation [7]. Of note, the FMSF device exhibits excellent reproducibility and reasonable agreement for repeated measurements [8].

To assess microvascular reactivity and endothelial function, the FMSF device measures the changes in the intensity of NADH fluorescence in the epidermis over time in response to brachial artery occlusion. Technically, FMSF registers two principal parameters: ischemic response (IR) and hyperemic response (HR). The parameter IR_{max} is defined as the ratio (in %) of relative to maximal baseline increase in NADH fluorescence intensity observed over occlusion, whereas IR_{index} is calculated as the area under the curve (AUC) of IR in relation to the baseline. Subsequently, the parameter HR_{max} is expressed (in %) as the relative to maximal baseline decrease in NADH fluorescence intensity during the reperfusion phase, while HR_{index} is defined as the AUC of the IR. When HR reflects microvascular reactivity and endothelial function, the IR may mirror tissue sensitivity to hypoxia (Fig. 1) [9].

Additionally, the FMSF device registers oscillations in the microcirculation, known as flowmotion, specifically present in skin microvascular blood flow. We distinguish endothelial, neurogenic, myogenic, respiratory, and cardiac oscillations based on the frequency analysis. There is compelling evidence that impaired flowmotion may be a symptom of various disorders, including diabetes, a broad spectrum of cardiovascular diseases, and autoimmune and infectious diseases such a COVID-19 [10].

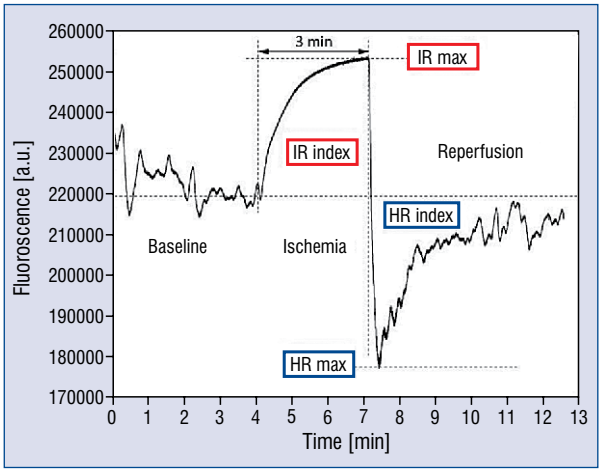

Figure 1. Exemplary image of nicotinamide adenine dinucleotide (NADH) fluorescence trace in response to blockage and release of blood flow in the brachial artery. The ischemic response (IR_{max} and IR_{index}) is relative to the baseline increase in NADH fluorescence intensity observed during occlusion, and the hyperemic response (HR_{max} and HR_{index}) is relative to baseline decrease in NADH fluorescence intensity over the reperfusion stage.

The direct measurement of oscillations during the reperfusion stage enables us to determine the hypoxia sensitivity (HS) parameter, which covers the intensity of flowmotion related to myogenic oscillations. Of note, myogenic oscillations are mainly stimulated on the reperfusion line following transient ischemia. Therefore, the HS parameter seems to be particularly significant to determine

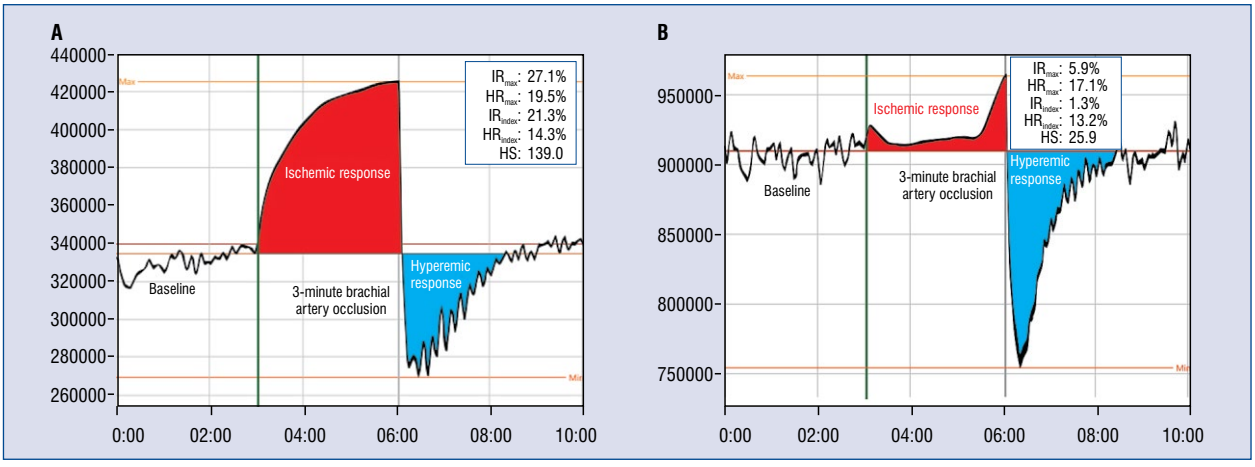

Figure 2. A. Typical image of nicotinamide adenine dinucleotide (NADH) fluorescence trace in a 30-year-old healthy subject with very high value of hypoxia sensitivity (HS) parameter as well as very dynamic ischemic (IR) and hyperemic responses (HR); **B.** Image of significant microvascular disturbances in NADH fluorescence trace in 30-year-old post-COVID patient with very low value of HS parameter as well as poor ischemic response (IR_{max} and IR_{index}).

the microcirculatory response to hypoxia. Interestingly, low HS values were related to a more severe course of COVID-19. Further, it was recently suggested that the microcirculatory response to hypoxia expressed as the HS parameter could be a prognostic factor in COVID-19 (Fig. 2A, B) [10].

Accumulating evidence suggests that we should consider COVID-19 as a systemic microvascular endothelial disease with different clinical manifestations from severe and acute to completely asymptomatic course [1, 2]. Therefore, non-invasive, sensitive, and reliable methods for microvascular endothelial function clinical monitoring are strongly needed.

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RESEARCH LETTER

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Synergistic effects of levosimendan and convalescence plasma as bailout strategy in acute cardiogenic shock in COVID-19: A case report

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Introduction

Novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been described to induce a variety of clinical conditions [1]. While some patients have flu-like symptoms only, others develop serious coronavirus disease 2019 (COVID-19), which has been associated with high inflammatory burden including vascular inflammation, myocarditis and cardiac arrhythmias that can result in cardiogenic shock (CS) [1]. CS in general is still a challenging disease [2], but in the context of COVID-19 associated CS, mortality is especially high and treatment recommendations or promising strategies are lacking.

Compassionate use of convalescence plasma is essayed in multiple centers today, but convalescence plasma alone does not comprise immediate CS stabilization. It has capabilities to prevent severe COVID-19 outbreak [3], but in COVID-19 associated CS many physicians are left blanked-faced because of widely lacking evidence.

Utilization of catecholamines in CS is accompanied by side effects and the use of mechanical circulatory support in CS is associated with risk of infection, bleeding, vessel or nerve injury [4]. Therefore, substitute and new therapeutic options are warranted, especially to manage hypoperfusion and concomitant organ failure [5]. Calcium sensitizer levosimendan was developed to enhance inotropy [2], but levosimendan is under debate because available trials do not reflect the initial drug's promises [5], while no trial has tested the impact of levosimendan in COVID-19 associated CS to date.

In this context, reported herein, is a first case on a breakthrough of COVID-19 induced CS using synergistic effects of levosimendan in addition to convalescence plasma therapy in an 84-year-old.

Case presentation

An 84-year-old female with cardiovascular disease, including transcatheter aortic valve replacement in 2019, permanent atrial fibrillation, heart failure and chronic renal failure was admitted complaining of shortness of breath, blood pressure 85/60 mmHg, heart rate 113/min. Rapidly, she developed high fever, non-productive cough and coronavirus polymerase chain reaction was positive for novel coronavirus SARS-CoV-2. The patient received 3 preparations of convalescence plasma (190–230 mL)

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Table 1. Laboratory parameters in COVID-19 cardiogenic shock.

Laboratory parameters	Addition of levosimendan in this COVID-19 patient				
	Day 1	Night 1	Day 2	Night 2	Day 3
Troponin	147	192	159	76	89
BUN [mg/dL]	94	128	123	75	72
Creatinine [mg/dL]	1.4	1.9	1.7	1.7	1.1
MDRD [mL/min]	36	25	29	47	53
GOT [U/L]	21	1540	560	607	537
GPT [U/L]	8	649	275	438	400
GGT [U/L]	105	239	93	160	150
LDH [U/L]	246	1240	599	534	497
Bilirubin [mg/dL]	2.23	1.54	3.32	1.03	0.93
Interleukin 6 [ng/L]	79	205	98	40	35
NT-proBNP [pg/mL]	12800	10800	10500	7290	2180
CRP [mg/dL]	8.4	11	10	8.9	6.0
Procalcitonin [ng/mL]	< 0.2	< 0.2	< 0.2	< 0.2	< 0.2
Blood gas analyses:					
pH	7.457	7.421	7.421	7.479	7.490
pCO_2 [mmHg]	34.0	25.6	26.6	28.4	30.1
HCO_3 [mmol/L]	24.4	17.2	19.5	23.0	24.7
Base excess	–0.9	–7.2	–2.5	–1.7	–0.4
Lactate [mmol/L]	3.9	6.7	8.6	4.1	1.5
$CVPO_2$ [mmHg]	34.6	26.1	43.2	46.8	53.8

BUN — blood urea nitrogen; CRP — C-reactive protein; $CVPO_2$ — central venous oxygen saturation; GGT — gamma-glutamyl transpeptidase; GOT — glutamic-oxaloacetic transaminase; GPT — glutamic-pyruvic transaminase; HCO_3 — bicarbonate; LDH — lactate dehydrogenase; MDRD — modification of diet in renal disease; NT-pro BNP — N-terminal pro-B-type natriuretic peptide; pCO_2 — partial pressure of carbon dioxide; pH — pH, decimal logarithm of the reciprocal of the hydrogen ion activity

on day 1, 3 and 5 after preexistent IgA and IgG antibodies had been excluded (anti-SARS-CoV--2-ELISA, EUROIMMUN AG, Lübeck, Germany).

Only hours after hospital admittance her hemodynamics rapidly deteriorated and she developed CS with severely impaired left ventricular function (LVEF 30%). Coronary angiography excluded coronary artery disease, developing COVID-19 associated CS.

Her clinical condition progressively deteriorated despite optimal guideline-derived CS medical treatment [2], with dyspnea at rest, tachypnea, orthopnea and cyanosis, requiring rising doses of intravenous inotrope drugs (dobutamine 8 μg/kg/min, norepinephrine 0.5 μg/kg/min). She developed systemic hypoperfusion syndrome resulting in multiple organ failure, high serum lactate levels and central venous oxygen saturation of 30% (Table 1).

At this time, available CS treatment options were exhausted and for further aggravation of COVID-19 induced CS, levosimendan was applied as a bailout compassionate therapy. After that, improvement in hemodynamics and clinical parameter eventuated (Table 1). Lactic acidosis came to regression and multiorgan failure slowly reversed. Given the life-threatening COVID-19 associated CS condition in this patient, add-on treatment with intravenous levosimendan 2.5 mg (12 μg/kg as bolus over 10 min and 0.1 μg/kg/min as infusion) adjunctive to convalescence plasma therapy resulted in improvement and finally breakthrough of COVID-19 associated CS, including clinical improvements, such as relief from dyspnea and orthopnea.

Discussion

According to available research, herein, is the first clinical in-vivo observation reported using the combined application of convalescence plasma and novel calcium sensitizer levosimendan to overcome acute CS in a COVID-19 patient. After 5 days of treatment the patient was stable enough to be discharged from intensive care unit and weeks after hospital admission she returned to her ordinary daily life.

We describe a novel treatment strategy for a complex clinically new disease pattern, with no verified therapy scheme known so far. During this life-threatening condition additional use of levosimendan resulted in potential synergistic effects resulting in hemodynamic stabilization and our strategy overcame CS not requiring invasive mechanical circulatory support (MCS), as MCS invasiveness in an 84-year-old carries notable risks such as bleeding, infection or thromboembolic complications [4, 6].

Moreover, levosimendan is currently the subject of intense discussion too, as this novel drug promises positive inotropic effects, but large clinical trials failed to confirm these effects [7]. European Society of Cardiology (ESC) guidelines recommend levosimendan in acute heart failure only to reverse effects of beta-blockade, if beta-blockade is considered to contribute to CS (evidence class IIb, level C) [2]. Furthermore, the drug may contribute to severe arrhythmia, myocardial ischemia and hypotension (evidence class I, level C). ESC guidelines recommend levosimendan only in combination with other established inotropes, such as dobutamine or vasopressors in CS [2] and levosimendan has undesired effects such as vasodilation and arrhythmia. In addition to that current goal in COVID-19 treatment is to reduce intravascular fluids to avoid mechanical ventilation while CS treatment often requires intravascular fluids. This relation seems incompatible and hemodynamic monitoring is challenging [8], why levosimendan use can only be understood as a bailout strategy.

Large randomized controlled trials such as the CHEETAH study investigated hemodynamic effects of levosimendan in 506 high-risk patients undergoing cardiac surgery, finding no benefit in terms of mortality or other clinical endpoints [5]. Similarly, the LEVO-CTS trial [9] or the LeoPARDS trial [10] found no benefit in comparison to placebo.

Besides available evidence, there is no randomized controlled clinical trial, nor any clinical evidence on how to manage therapy-refractory COVID-19 CS, because our first in-vivo observation of synergistic effects for the combination of levosimendan and plasma therapy brings the hypothesis that levosimendan may be an option in critical COVID-19 induced CS [5]. Synergistic effects may derive from the timely critical combination of the immune system response through convalescence plasma therapy, but which requires hemodynamic stability and sufficient circulation that may have been provided through levosimendan application. This engaged synergy appears to have facilitation of breakthrough of COVID-19 CS in our presented case.

However, additional research is needed to better define indications for, and benefits of, levosimendan therapy. Nevertheless, studies of COVID-19 CS patients are difficult to conduct, but scientific data is important to provide assistance on how to best treat COVID-19 CS patients and whether levosimendan application in combination with other therapeutics might lead to similar benefits as observed in our reported case.

Ethics statement

An exemption of ethical approval has been assigned for reporting this case and this report is in accordance with the Declaration of Helsinki.

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Cardiac magnetic resonance characteristics of acute myocarditis occurring after mRNA-based COVID-19 vaccines immunization

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Almost 1 billon people worldwide have been fully vaccinated. Recent publications report on several cases of presumably vaccine-induced myocarditis [1–3]. This article presents a series of patients with this condition.

Case 1. A 29-year-old male presented with severe chest tightness, dyspnea and retrosternal pain radiating to the left arm 2 days after receiving Spikevax Vaccine Moderna. Resting electrocardiogram (ECG) revealed pattern typical for cardiac muscle injury, alongside with increased inflammation parameters (peak C-reactive protein [CRP] of 39 mg/L, peak troponin I above 50 ng/mL). Echocardiography revealed normal cardiac function with left ventricular ejection fraction (LVEF) of 65% and tricuspid annular plane systolic excursion (TAPSE) of 23 mm. Acute coronary syndrome and pulmonary embolism were excluded with coronary angiography and computed tomography, respectively. On the 7th day after vaccination, cardiac magnetic resonance (CMR) was performed, revealing LVEF of 62% and signs of edema and acute muscle injury in inferior, infero-lateral and antero-lateral segments. Subepicardial/intramural late gadolinium enhancement (LGE) was also found in the same regions, corresponding to the extent of edema. No viral diagnostics were performed.

Case 2. A 12-year-old male presented with severe stabbing chest pain, diarrhea and fever 2 days after receiving Comirnaty vaccine. Resting ECG revealed a pattern typical for cardiac muscle injury (ST elevation in leads I, II, V3–V6), alongside with increased inflammation parameters (peak CRP of 23 mg/L, peak troponin I of 5.1 ng/mL). On the 3rd day after vaccination LVEF of 58% and TAPSE of 18 mm were noted in echocardiography. On the 4th day, CMR was performed, revealing EF of 56% and subepicardial/intramural LGE in the basal infero-lateral and basal inferior wall. In extended viral diagnostics with polymerase chain reaction (PCR) and serology methods no infectious cause of myocarditis was found. No lymphocyte populations abnormalities were found. The patient required only analgesic treatment (paracetamol) during 1st day of hospitalization. Day 5 evaluation showed improved systolic function (LVEF 72%, TAPSE 25 mm).

Case 3. A 17-year-old male presented with severe stabbing chest pain and fever 1 day after receiving Comirnaty vaccine. Resting ECG revealed pattern typical for cardiac muscle injury (ST elevation in leads II, III, aVF), alongside with increased inflammation parameters (peak CRP of 18.2 mg/L, peak troponin I 8.9 ng/mL). In echocardiography on the 2nd day after vaccination LVEF of 63% and TAPSE of 26 mm were described. In the follow-up ECG evaluation T waves inversion in leads II, III, aVF, V6 was observed. On the 6th day CMR was performed, revealing EF of 60% and subepicardial features of edema/acute injury as well as LGE areas in the basal and mid-ventricular infero-lateral and inferior segments. In extended viral diagnostics

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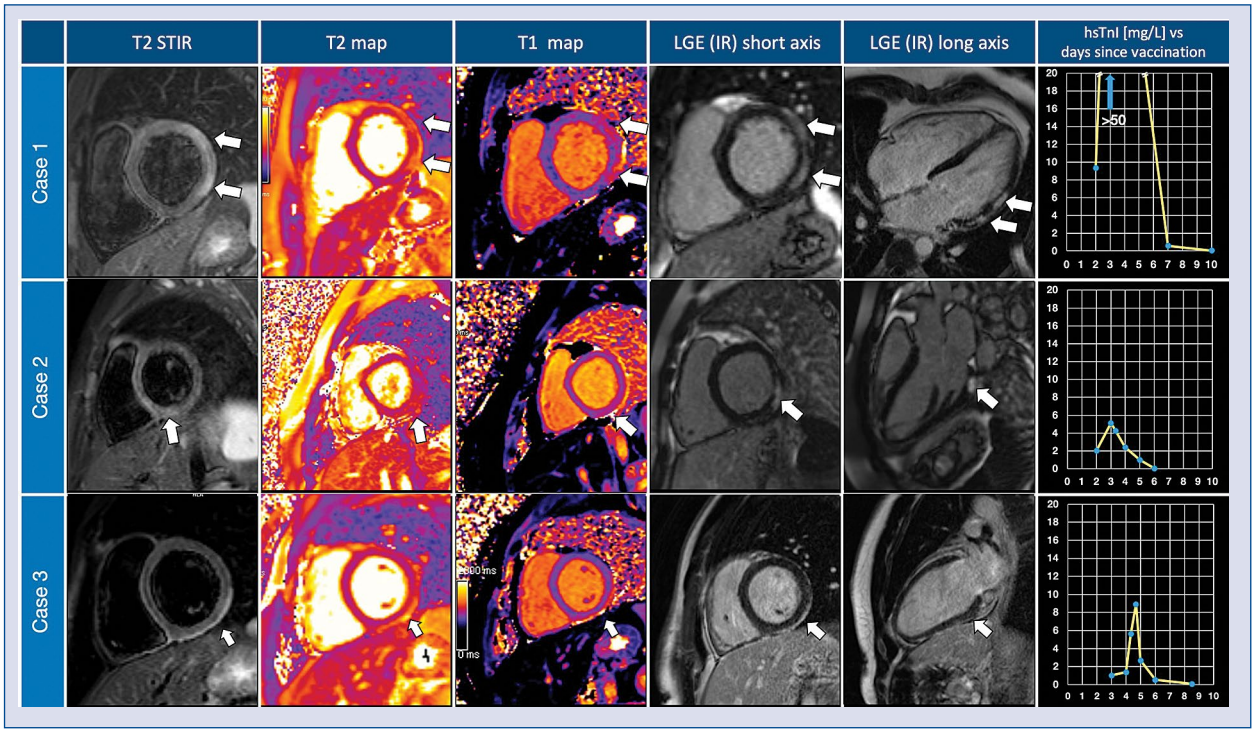

Figure 1. Case 1. Subepicardial hyperintensity consistent with edema (i.e., features of acute injury) in the basal inferior, infero-lateral and antero-lateral segments in the T2-weighted short tau inversion recovery (STIR) image, paralleled by increased T2 and T1 relaxation times in parametric mapping and a matching late gadolinium enhancement (LGE) area suggestive of irreversible damage (arrows); **Case 2.** Mild localized edema found in the basal inferior and infero-lateral segments in the T2 STIR image, again paralleled by increased T2 and T1 relaxation times and a small LGE patch found solely in the basal infero-lateral segment (arrows); **Case 3.** Mild subepicardial edema in T2 STIR closely matched by T1 and T2 increase in parametric mapping, as well as subtle subepicardial LGE in the basal inferior and infero-lateral segments (arrows); IR — inversion recovery; hsTnI — high sensitivity troponin I plasma levels by days since vaccination.

with PCR and serology methods, no infectious agents were found. Lymphocyte populations were normal.

The current patients have several common characteristics. All three were young males and had no comorbidities. In all three, myocarditis developed shortly after the 2nd dose of mRNA vaccine against coronavirus disease 2019 (COVID-19), within 1 to 5 days. None of the patients had a history of previous COVID-19 disease. All of them presented with elevated troponin levels, peaking on the 3rd or 4th day after vaccination. Apart from the troponin, CK-MB mass, liver enzymes and CRP were elevated in all patients. No other laboratory abnormalities were found. On echocardiography the LVEF was within the normal range in all of these cases and no regional wall motion abnormalities were found. Interestingly, in all three subjects CMR revealed a similar pattern of myocardial injury found predominantly in the inferior and inferolateral segments (Fig. 1). This pattern included localized features of subepicardial edema in T2-weighted short tau inversion recovery (STIR) images, accompanied by elevated native T1 and T2 relaxation times in cardiac parametric mapping, with corresponding foci of LGE (i.e., areas of predominantly irreversible myocardial injury) in the respective regions. The clinical course was favorable in all three cases. They only transiently received analgesia (paracetamol). The hospital course ranged from 5 to 9 days (9, 5, 5, respectively). All had normalization of ECG and laboratory parameters, were asymptomatic and in good general condition on discharge.

Noticeably, no similar cases were reported in the course of registration trials of any of the vaccines [4, 5]. This might be due to the low incidence of this adverse effect. So far, in the documented region, with over 450,000 fully vaccinated inhabitants, only 3 (0.0007%) cases of vaccine-induced myocarditis have been identified. Similarly, in Israel, the development of myocarditis within 30 days from the vaccination was reported in 121 subjects per over 5 million fully vaccinated

citizens (0.002%). The present series includes only male patients, concordantly with the published reports also showing male predominance [2, 6].

The causal relation between myocarditis and COVID-19 vaccination has not been proven. However, the time concordance is quite indicative. Also, the mechanism responsible for triggering this adverse reaction has not been explained. The subjects with post-vaccine myocarditis do not present abnormally elevated anti-COVID-19 antibodies nor other laboratory markers that could differentiate them from patients suffering from viral myocarditis [2, 7, 8]. The current findings are consistent with previous reports.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can cause damage to the myocardium in two possible ways: primarily, by direct myocyte injury after binding to angiotensin--converting enzyme 2 (ACE-2) receptor [2], but also in the late phase of infection, in the process of cytokine storm [9]. Given that the post-vaccine myocarditis occurs predominantly after the second dose of mRNA specimen, which causes greater lymphocyte activation [10], it is more likely to be immune-mediated than related directly to the injected substance, however the precise pathway remains unknown. Contrary to a previous report [7] we found normal lymphocyte distributions in one and mildly elevated NK level in the second one (the first one was not assessed).

At present, unquestionable benefits of anti--COVID-19 vaccines outweigh the low risk of developing myocarditis that is mild and transient and should not be considered a reason to withhold vaccine administration. This has been clearly stated by the Advisory Committee on Immunization Practices [10]. Further research is necessary to investigate the pathomechanism of this adverse reaction, identify subjects at risk and implement adequate means of prevention.

Conflict of interest: None declared

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Pulmonary arterial hypertension and right ventricular systolic dysfunction in COVID-19 survivors

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Although much has been published about the in-hospital prognosis of COVID-19 patients, much less attention has been paid to what happens to those who have been discharged alive from the hospital [1]. In the present study we investigated a group of patients initially admitted for acute respiratory failure due to coronavirus disease 2019 (COVID-19)-related interstitial pneumonia and then, at a later time point, discharged from hospital. We noted that some of these patients presented a specific cluster of signs and symptoms: asthenia, fatigue, high heart rate (HR) at rest, and tachycardia disproportionate to physical exertion [2]. These patients find it difficult to resume their social and working life after discharge. We can say that these symptoms and signs fall within the generic definition of "post-COVID syndrome" [3], but we do not know the origin and causes of this clinical condition. We then performed a right heart catheterization (RHC) in all these patients, in order to evaluate the possible presence of cardiac and/or pulmonary vascular alterations.

The study group consisted of 25 consecutive patients, COVID-19 survivors, referred to our divisional outpatient clinic for the cluster of signs and symptoms described above. All patients were hospitalized between March 2020 and February 2021. In all these patients we performed a RHC and a 6-minute walking test (6MWT). The obtained results were compared with those of a control group, which comprised 25 gender- and age-matched patients, COVID-19 survived, but asymptomatic.

Patients with pulmonary hypertension (PH) underwent an additional 6MWT and catheterization every 6 months of follow-up.

The present study was approved by the local Ethical Committee (protocol number: AOU 0012597).

Right heart catheterization was performed using a 7 F balloon-tipped (Swan-Ganz catheter), triple lumen thermodilution catheters. Right atrial pressure (RAP), mean pulmonary artery pressure (mPAP), and pulmonary capillary wedge pressure (PCWP) were recorded. Cardiac output (CO) was determined by thermodilution method. Cardiac index (CI = CO/body surface area), right ventricle stroke volume (RVSV = CO/HR), and pulmonary vascular resistance [PVR = (mPAP − PCWP)/CO] were calculated. Right ventriculography was performed in the 30° right anterior oblique view using a 6 F pig-tail catheter. Right ventricular (RV) end-diastolic diameter (EDD) and ejection fraction (EF) were calculated.

Continuous variables were expressed as mean ± ± standard deviation or median (range) values, and categorical data as percentages. All dichotomous variables were compared applying the χ^2 test; continuous variables using one-way analysis of variance. Changes from baseline to follow-up were assessed using analysis of variance for repeated measures. Bonferroni's correction was utilized for multiple comparisons. $P < 0.05$ was considered statistically significant.

Our study population comprised 25 patients hospitalized for acute respiratory failure due to

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Table 1. Comparison between symptomatic (study group) and asymptomatic (control group) post-COVID-19 patients. Both groups consisted of patients who survived SARS-CoV-2 infection, but only patients included in the study group suffered from the specific cluster of the following signs and symptoms: asthenia, fatigue, elevated heart rate at rest, and tachycardia disproportionate to exertion. The control group consisted of asymptomatic patients of equal age and gender.

Parameter	Control (asymptomatic) group (n = 25)	Study (symptomatic) group (n = 25)	P
Age [years]	64 ± 4	64 ± 5	0.9
Male gender	72% (n = 18)	72% (n = 18)	1
BSA [m^2]	2.1 ± 0.5	2.4 ± 0.6	0.8
BMI [kg/m^2]	26.7 ± 2.7	27.6 ± 2.6	0.6
SBP [mmHg]	125 ± 9	110 ± 8	0.01
DBP [mmHg]	74 ± 7	78 ± 9	0.01
WHO functional class:			0.0001
0	100% (n = 25)	0	
I	0	0	
II	0	24% (n = 6)	
III	0	76% (n = 19)	
IV	0	0	
6MWT [m]	590 ± 40	420 ± 45	0.0001
HR at rest [bpm]	73 ± 14	91 ± 10	0.001
HR peak, on maximum physical effort [bpm]	110 ± 13	135 ± 17	0.001
Echocardiographic and Doppler parameters			
RV EDD (basal) [mm]	45 ± 8	55 ± 9	0.001
RV:LV ratio	0.9 ± 0.3	1.2 ± 0.3	0.01
RV length [mm]	62 ± 13	71 ± 14	0.03
RVOT diameter [mm]	30 ± 7	32 ± 8	0.3
TAPSE [mm]	23 ± 3	16 ± 3	0.001
SPAP [mmHg]	26 ± 4	42 ± 5	0.001
RV EF (3D) [%]	50 ± 5	41 ± 6	0.001
RA area [cm^2]	13 ± 4	19 ± 3	0.001
Hemodynamic parameters			
mRAP [mmHg]	4 ± 2	11 ± 3	0.001
mPAP [mmHg]	16 ± 3 (range: 13–19)	23 ± 2 (range: 21–27)	0.01
PCWP [mmHg]	9 ± 2	8 ± 2	0.8
mRAP/PCWP	0.44 ± 0.22	1.38 ± 0.29	0.0001
PVR [Wood Unit]	1.5 ± 0.6	3.1 ± 0.7	0.01
CI [$L/min/m^2$]	2.7 ± 0.6	2.2 ± 0.4	0.01
RV SV [mL/beat]	77 ± 16	59 ± 14	0.001
RV EDD [mm]	48 ± 13	59 ± 12	0.001
RV EF [%]	55 ± 9	43 ± 9	0.001

BMI — body mass index; BSA — body surface area; CI — cardiac index; DBP — diastolic blood pressure; HR — heart rate; LV — left ventricle; mPAP — mean pulmonary artery pressure; mRAP — mean right atrial pressure; PCWP — pulmonary capillary wedge pressure; PVR — pulmonary vascular resistance; RA — right atrium; RV — right ventricle; RV EDD — right ventricular end-diastolic diameter; RV EF — right ventricular ejection fraction; RVOT — right ventricular outflow tract; RV SV — right ventricular stroke volume; SBP — systolic blood pressure; SPAP — systolic pulmonary artery pressure; WHO — World Health Organization; 6MWT — 6-minute walking test

COVID-19 interstitial pneumonia, confirmed by chest computed tomography images.

The comparison between symptomatic patients and the control group is depicted in Table 1.

Twenty-one patients/25 (84% of the entire population) had an additional control after 6 months, and 15/25 (60%) one more after 1 year of follow-up. In these patients we noted a significant improve-

ment in pulmonary pressure (mPAP passed from 23 ± 2 to 20 ± 4 mmHg after 6 months, to 18 ± ± 5 mmHg after 1 year of follow-up; p = 0.01 for all comparisons); a significant increase in RV systolic performance (RVSV moved from 59 ± 8 to 66 ± ± 10 mL at 6 months, and 72 ± 12 mL after 1 year; p = 0.01); associated with a significant amelioration of 6MWT (from 420 ± 45 to 495 ± 40 m after 6 months, to 520 ± 35 m after 1 year; p = 0.001).

All patients who presented the following cluster of signs/symptoms: asthenia, fatigue, high HR at rest, and tachycardia disproportionate to physical exertion, suffered from mild degree pulmonary arterial hypertension (PAH) and severe RV systolic dysfunction. We found a perfect match between this hemodynamic status and the described clinical condition.

All our symptomatic patients presented a mPAP > 20 mmHg, a value already indicative of PH according to the 6th World Symposium on Pulmonary Hypertension of Nice, 2018 [4]. In addition, RVSV and EF were both reduced by about 40% compared to the asymptomatic (control) group.

Our hypothesis would be that, in relation to the parenchymal ("ground-glass" and "dense" opacifications) and vascular pulmonary involvement (markedly impaired pulmonary perfusion, caused by pulmonary angiopathy and thrombosis) that occurs during the acute phase of pneumonia [5, 6], an increase in PVR develops, with a consequent onset of PH [7]. RV normally works at an extremely low level of afterload, and the muscle thickness of its free wall is not particularly conspicuous. However, when the RV is stressed by an increase in afterload, its internal cavity gradually expands [8, 9]. In this phase of the disease, the right atrium acts as an effective pump in the late diastole. The pressure in the right atrium consequently increases. The intensification of the right atrium contractile efficiency implies a recruitment of preload, which has the function of more effectively filling the underlying ventricle. According to the Frank-Starling principle, the RV increases the stroke volume [9].

Furthermore, the most important and timely compensatory mechanism capable of maintaining an adequate CO, represented by the stimulation of the sympathetic-adrenaline reflex, becomes active from the earliest stages of the disease, which leads to positive chronotropic and inotropic effects [10].

In conclusion, there is a phase of COVID-19, after discharge, characterized by PAH and RV systolic dysfunction. As long as this state persists, patients suffer from a specific cluster of symptoms and signs.

Our results allow us to assume that recovery of normal RV function is gradual and spontaneous. In other words, the RV initially sustains an increase in pulmonary resistance, and then gradually resumes its function, as after a "stunning". However, it is noticeable that the disappearance of symptoms is always accompanied by improvement of the RV systolic performance.

Conflict of interest: None declared

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Does canagliflozin decrease natriuretic peptide levels in patients with diabetes and heart failure?

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Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have recently been introduced as an oral antidiabetic therapy; proving to be safe and showing a reduction in the risk of cardiovascular events in patients with type 2 diabetes (T2D) [1–3], especially in terms of hospitalization for heart failure (HF). In a recent study, DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial [4], in which patients with chronic HF and reduced ejection fraction with and without diabetes were included; dapagliflozin demonstrated a reduction in the composite primary outcome (hospitalization or an urgent visit resulting in intravenous therapy for HF and death from cardiovascular causes) and death from any cause. Several mechanisms have been proposed to explain the benefit of SGLT2i, such as improvement in loading conditions, cardiac metabolism and bioenergetics, inhibition of myocardial Na^+/H^+ exchange, reduction of cardiac fibrosis or alteration in adipokines and vascular function [5].

The DEFINE-HF (Dapagliflozin Effects on Biomarkers, Symptoms and Functional Status in Patients with HF with Reduced Ejection Fraction) trial [6] has suggested that the benefit of dapagliflozin in patients with chronic HF does not depend on the natriuretic peptide pathway, considering that dapagliflozin did not significantly reduce N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels over 12 weeks as compared with placebo. Nonetheless, these results have been controversial; an analysis of DAPA-HF trial has demonstrated a reduction of median NT-proBNP from baseline to 8 months with dapagliflozin (–303 pg/mL). With respect to canagliflozin, a post hoc analysis of the CANVAS (Canagliflozin Cardiovascular Assessment Study) Program with 666 patients showed that NT-proBNP concentration did not increase in the canagliflozin group, and it did slightly in the control group over a 2-year follow-up and from a baseline median of 47 pg/mL [7].

Additionally, there are limited data of the effect of SGLT2i in patients after hospitalization for HF. In the pilot randomized study EMPA-RESPONSE-AHF (Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure) [8], patients admitted for HF with or without T2D were randomized to empagliflozin 10 mg/day or placebo and no differences were observed in NT-proBNP concentrations and other primary outcomes at 60-days follow-up.

The present study is a retrospective cohort study which included all consecutive patients with T2D admitted for HF from January 2017 to December 2019 in a single center. This study was conducted according to the Declaration of Helsinki and was approved by Local Clinical Research Ethics Committee with the code GC-15-2017-001. Excluded patients were those in whom treatment with SGLT2i was contraindicated, patients with chronic kidney disease stage 3b or higher (eGFR < 45 mL/min/1.73 m^2) and those receiving other SGLT2i than canagliflozin at discharge. All patients had received a primary diagnosis of acute decompensated HF, including signs and symptoms of fluid overload and a concentration of NT-proBNP of at least 1400 pg/mL. The addition of canagliflozin and the starting dose

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Table 1. Baseline characteristics.

Characteristic	Canagliflozin (n = 45)	Control (n = 57)	P
Age	69 ± 10	73 ± 11	0.04
Female sex	15 (33.3%)	30 (52.6%)	0.05
Body mass index [kg/m^2]	31.9 ± 5.1	30 ± 4.4	0.14
Hypertension	37 (82.2%)	48 (84.2%)	0.79
Atrial fibrillation or flutter	13 (28.9%)	20 (35.1%)	0.66
Coronary artery disease	11 (24.4%)	17 (29.8%)	0.55
Chronic obstructive pulmonary disease	11 (24.4%)	8 (14%)	0.18
Previous functional class (NYHA):			
I–II	38 (84.4%)	50 (87.7%)	0.7
III–IV	7 (15.6%)	7 (12.3%)	
Previous hospitalization for HF	15 (33.3%)	27 (47.4%)	0.15
Clinical features of HF:			
Ejection fraction ≤ 40%	26 (57.8%)	31 (54.4%)	0.73
Ischemic cause	17 (37.8%)	16 (28.1%)	0.32
Killip class on admission:			
I–II	35 (77.8%)	44 (77.2%)	0.94
III–IV	10 (22.2%)	13 (22.8%)	
Serum creatinine [mg/dL]	1.07 ± 0.3	1.1 ± 0.4	0.92
Estimated GFR [mL/min/1.73 m^2]	69.7 ± 24.4	68.6 ± 26.3	0.82
Hemoglobin [g/dL]	12.7 ± 2	12.3 ± 2.3	0.31
Glycated hemoglobin	7.4 ± 1.5	6.8 ± 2.5	0.16
Device therapy:			
ICD	1 (2.4%)	4 (8.7%)	0.21
CRT	0 (0%)	3 (6.5%)	0.1
HF treatment at hospital discharge:			
ACE inhibitor	21 (46.6%)	12 (21.5%)	0.02
ARB	17 (37.7%)	32 (56.2%)	0.16
ARN inhibitor	7 (15.6%)	8 (14%)	0.83
Beta-blocker	35 (78.8%)	45 (78.9%)	0.9
MRA	26 (57.8%)	30 (52.7%)	0.67
Loop diuretic	35 (77.7%)	46 (80.7%)	0.66
Digoxin	6 (13.3%)	14 (24.6%)	0.16
Glucose-lowering medication:			
Biguanide	35 (77.8%)	43 (75.4%)	0.78
Sulfonylurea	2 (4.4%)	4 (7%)	0.58
DPP-4 inhibitor	3 (6.7%)	12 (21.1%)	0.04
GLP-1 receptor agonist	1 (2.2%)	5 (8.8%)	0.16
Insulin	12 (26.7%)	22 (38.6%)	0.26

Numeric values are expressed as median (interquartile range) or number (percentage, %). ACE —angiotensin-converting enzyme; ARB — angiotensin receptor blocker; ARN — angiotensin receptor neprilysin; CRT — cardiac resynchronization therapy; DPP-4 — dipeptidyl peptidase 4; GFR — glomerular filtration rate; GLP-1 — glucagon-like peptide 1; HF — heart failure; ICD — implantable cardioverter-defibrillator; MRA — mineralocorticoid receptor antagonist; NYHA — New York Heart Association

were left to criteria of the treating physician. NT-proBNP concentrations were collected at 3 months, 6 months, and 1 year after hospitalization from laboratory records if available.

The aim of this study was to compare mean NT-proBNP levels at hospital discharge and at 3, 6 and 12 months of follow-up in patients treated with and without canagliflozin.

Table 2. N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels during follow-up period according to canagliflozin.

Group	Admission	Discharge	3 months	6 months	12 months	P*
Canagliflozin (n = 45)	6279 ± 5446 (3110–7884)	4406 ± 3341 (1317–7031)	1376 ± 1266 (491–1638)	1350 ± 1246 (359–1927)	1612 ± 1891 (400–1856)	
Control (n = 57)	6969 ± 7753 (2052–10197)	5587 ± 5358 (2364–6117)	3223 ± 3201 (846–4650)	4106 ± 5011 (733–5040)	4702 ± 6036 (1346–5426)	
P**	**0.692**	**0.258**	**0.001**	**0.001**	**0.003**	**0.004**

NT-proBNP levels are expressed as mean ± standard deviation and interquartile range (IQR 25–75). *Comparing p-value of NT-proBNP levels between the canagliflozin group and the control group during follow-up period (repeated-measures ANOVA analysis). **Comparing p-value of NT-proBNP levels between the canagliflozin group and the control group por each period of follow-up (Student t-test).

This study was conducted according to the Declaration of Helsinki and was approved by Local Clinical Research Ethics Committee (Hospital Universitario Reina Sofía). Written informed consent was obtained from all patients.

Continuous variables are expressed as the mean ± standard deviation or median (interquartile range: IQR 25–75) and were compared using the Student t-test or the Mann–Whitney U test, according to the distribution, which was tested by the Saphiro-Wilk test.

Categorical variables are presented as counts and percentages and were compared using the χ^2 test or the Fisher exact test, as appropriate. Changes in NT-proBNP concentration during follow-up were compared with repeated-measures ANOVA analysis. A value of $p < 0.05$ was considered statistically significant.

A total of 102 patients were included: 45 patients (starting dose: 57.8%, 100 mg/day and 42.2%, 300 mg/day) in the canagliflozin group and 57 patients in the control group. No serious adverse events among patients who received canagliflozin were detected. Three patients discontinued canagliflozin during follow-up, two of them due to hypotension and one by medical criteria. Table 1 summarizes the baseline clinical characteristics of the patients. There were no significant differences in clinical characteristics and comorbidities in both groups, except for age; slightly lower in the canagliflozin group (69.2 ± 10.3 vs. 73.2 ± 11.1; $p = 0.04$). Treatment at discharge was also similar, patients in the control group received more dipeptidyl peptidase-4 inhibitors (21.1% vs. 6.7%; $p = 0.04$). Few patients received sacubitril-valsartan (15.6%) in the canagliflozin group and 14% in the control group. More than a half of the patients in both groups had HF with reduced ejection fraction, 26 (57.8%) in the canagliflozin group and 31 (54.4%) in the control group.

Table 2 shows the results of the analysis of NT-proBNP concentration levels at admission, discharge and at 3, 6 and 12 months of follow-up. Mean levels of peptides were similar in both groups at hospital admission and discharge. During the first 3-month period, a decrease in NT-proBNP concentration was observed in both groups. This decrease was more pronounced in the canagliflozin group ($p < 0.001$). At 6 and 12 months, NT-proBNP levels remained stable in patients treated with canagliflozin, in contrast with patients in the control group, in whom mean levels increased. Consequently, after a year of follow-up, the difference in NT-proBNP levels between groups was more evident ($p = 0.003$), with a reduction from baseline of 64.3% in the canagliflozin group and of 15.8% in control group ($p = 0.004$). There were no differences in patients according to the ejection fraction group.

Notwithstanding, the limitations inherent to the observational study design, we observed an early significant reduction in NT-proBNP levels that was sustained for at least 12 months after discharge. In addition, this reduction was equally observed in patients with reduced and preserved ejection fraction HF.

Since the diuretic effect of SGLT2i does not seem to be enough to explain these differences and the other multiple cardiovascular benefits, ongoing studies are trying to elucidate the potential mechanisms involved: improved myocardial energetics and ionic homeostasis, adipokine regulation, cardiac remodeling, etc. [9]. All these cardiac mechanisms and the increasingly accounted for protective renal effects could be related to the observed reduction in NT-proBNP levels during follow-up.

The present findings support the controversial idea that SGLT2i reduces NT-proBNP levels in patients with HF; and may contribute to building the growing knowledge about SGLT2i mechanisms.

In conclusion, a canagliflozin prescription at discharge in patients with HF and T2D was associated with a reduction in NT-proBNP concentration at follow-up. Future clinical randomized trials should be performed to confirm these findings.

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VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

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Cardiac tamponade caused by an ectopic intrapericardial thymic carcinoma

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A 69-year-old man was referred to our institute with slight dyspnea. Echocardiography showed a giant mass that occupied the pericardial cavity. 2-[18F]-fluoro-2-deoxy-D-glucose (^{18}F-FDG) positron emission tomography/magnetic resonance imaging (PET/MRI) revealed the mass (7 × 4 cm) with low intensity on T1 weighted imaging, high intensity on T2 weighted imaging and diffusion weighted imaging (b = 800) **(Suppl. Fig. S1A–C)**. PET/computed tomography (PET/CT) showed that the mass was FDG avid with the maximum standardized uptake value (SUV_{max}) being 12.4 (**Suppl. Fig. S1D**). The patient refused surgery. Nine months later, he was delivered to our institute due to the presence of symptoms of cardiac tamponade. PET/CT showed an increased size (10 × 7 cm) and FDG uptake (SUV_{max} = 17.7) of the mass (Fig. 1A). CT angiography exhibited the presence of massive pericardial effusion (Fig. 1B).

Through a median sternotomy, the surgeon found that the mass was completely located in the pericardial cavity. The mass underwent radical resection, and the invaded superior vena cava and right atrium was reconstructed using a bovine pericardial patch under cardiopulmonary bypass (Fig. 1C, D). The patient felt symptomatic relief and was referred to oncologists to receive adjuvant therapy. Histopathology showed that the tumor consisted of epithelial cells (Fig. 1E, i) with positive immunostaining of CD5, CD117 and P63 (Fig. 1E, ii–iv). These supported a diagnosis of ectopic thymic carcinoma (type C), which could have originated from aberrant thymic tissue left behind in pericardium during embryologic development of thymic gland. The patient has survived for over 14 months and further follow-up is ongoing.

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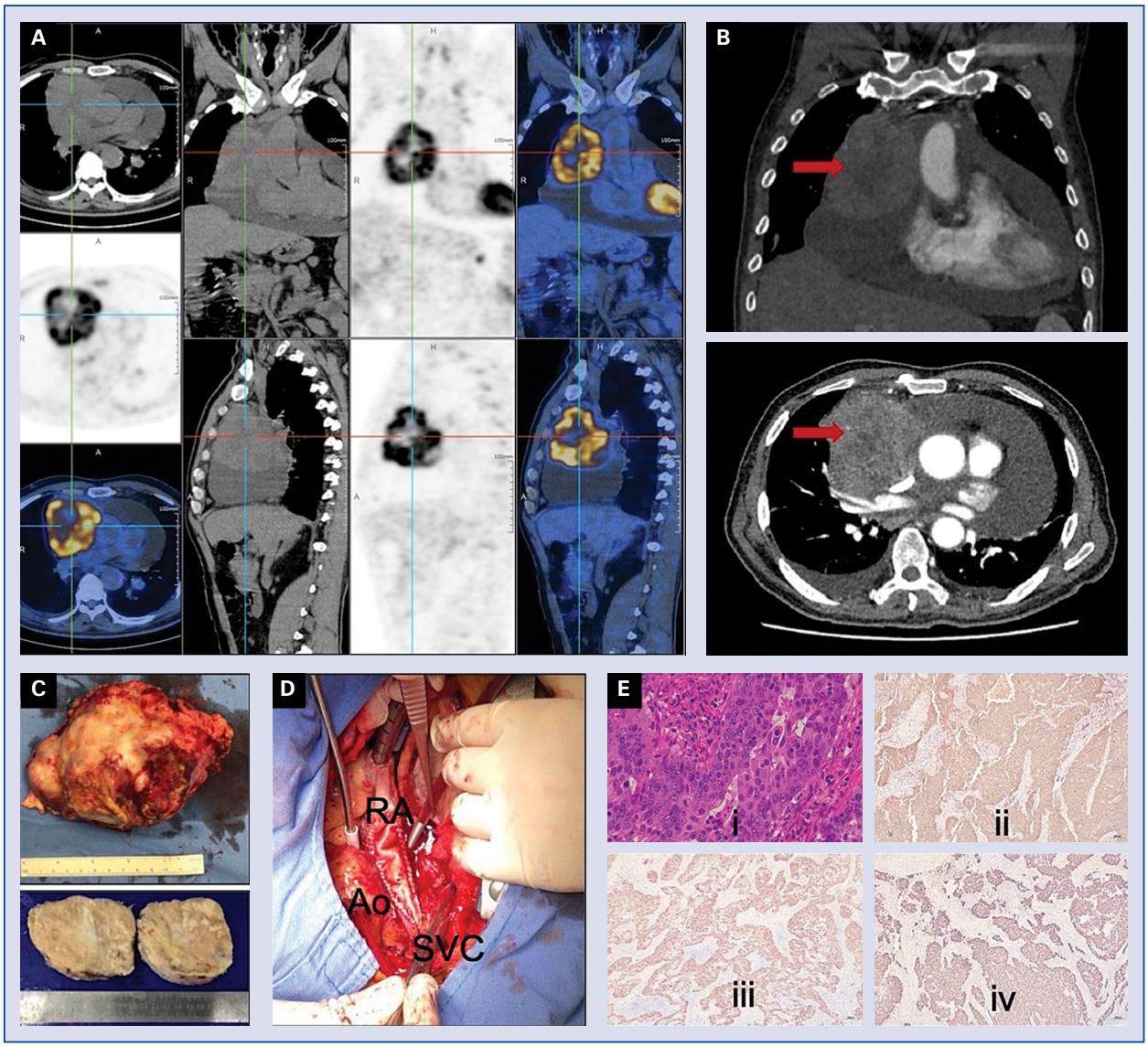

Figure 1. A. Positron emission tomography/computed tomography showed high avidity of the intrapericardial mass; **B.** Computed tomography angiography presented a close relationship between the mass (arrow) and surrounding structures. The mass was en bloc resected (**C**), and right atrium (RA) and superior vena cava (SVC) were reconstructed (**D**); **E.** Hematoxylin and eosin (i) and immunohistochemical staining for CD5 (ii), CD117 (iii) and P63 (iv) of the mass; Ao — ascending aorta.

VIA MEDICA

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Conduction system engagement by mid-septal leadless pacemaker in a patient with persistent iatrogenic atrioventricular block

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An 89-year-old woman was admitted to our Arrhythmology Unit for syncope. Electrocardiogram (ECG) showed sinus rhythm with left bundle branch block (LBBB) (Fig. 1A). Holter ECG monitoring showed paroxysmal atrial fibrillation with difficult rate control. The patient was referred for 'ablate and pace' strategy. Left subclavian vein occlusion prevented the traditional pacing implant. Micra™ TPS was implanted in the right ventricle mid-septal position causing right bundle branch (RBB) bump and atrioventricular block that was promptly treated with a temporary pacing wire (Fig. 1B). Micra™ was successfully deployed (Fig. 1C, D). Pacing threshold was 0.50 V @ 0.24 ms, sensing was 6.4 mV and impedance was 610 Ohm. Pacemaker dependency was persistent. Paced QRS was identical in morphology and duration to baseline QRS: duration of 130 ms, rS complex in inferior leads, positive R wave in lead I and aVL with a typical notch at the onset of QRS (Fig. 1E). Pacing at high output (5 Volt @ 1 ms) did not change QRS morphology (Fig. 1F). There are two possible explanations of this phenomenon: 1) the different localizations between the site of RBB induced block and Micra™ pacing site, with potential selective activation of the right bundle; 2) the greater surface of endocardial contact of the Micra™ resulted in the capture of a greater portion of conduction tissue fibers connected downstream from the site of RBB block. The ability of Micra™ leadless pacemakers to selectively pace the conduction system could allow remarkable advantages in terms of QRS duration.

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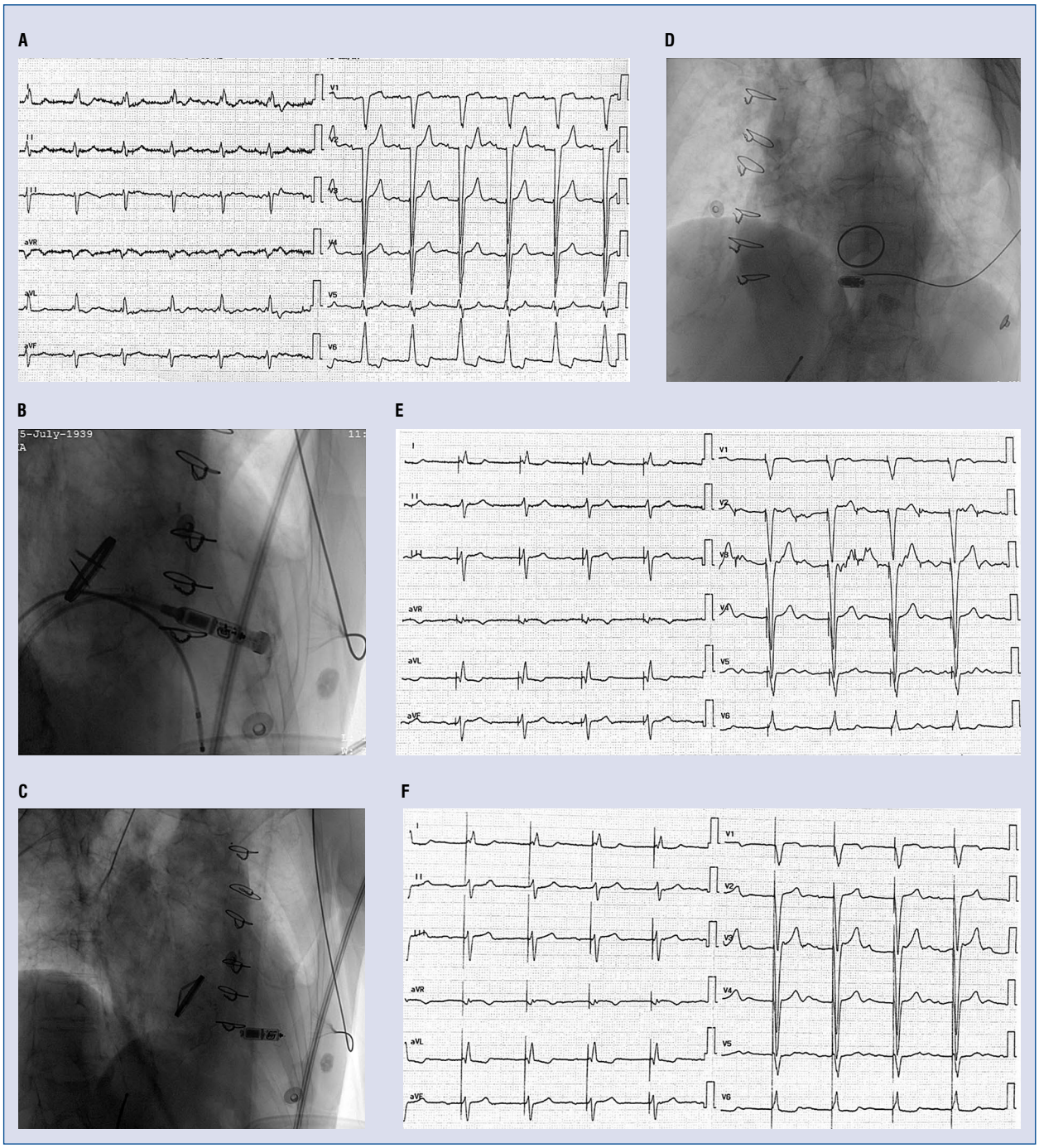

Figure 1. Micra™ implantation and paced electrocardiogram (ECG); **A.** Baseline 12 lead ECG at admission; **B.** Right anterior oblique view of Micra™ implantation and temporary pacing lead; **C, D.** Right and left anterior oblique view of Micra™ system successfully deployed at right ventricle mid-septum; **E.** 12 lead ECG after Micra™ implantation with pacing at 2.5 V @ 0.4 ms; **F.** 12 lead ECG with pacing at 5 V @ 1 ms. The panels B, C and D show the mechanical valve 27 SJM Regent previously implanted in the mitral position.

VIA MEDICA

LETTER TO THE EDITOR

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Need to update cardiological guidelines to prevent COVID-19 related myocardial infarction and ischemic stroke

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This paper was guest edited by Prof. Togay Evrin

Novel coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a challenge for the health care system worldwide and continues to have a significant impact on both the lives of people around the world and the functioning of medical services [1, 2]. One-third of patients hospitalized due to severe coronavirus disease 2019 (COVID-19) develops macrovascular thrombotic complications, including venous thromboembolism, myocardial injury/infarction, and stroke [3]. Both the risk of stroke and myocardial infarction caused by COVID-19 has posed huge pressures on medical services during the pandemic. Beyond the COVID-19 pandemic period itself, the post-pandemic effects can also be dramatic for healthcare systems, because rehabilitation services shall manage patients recovering from severe COVID-19 with post-intensive care syndromes, which results in physical deconditioning and cognitive impairments, patients with comorbid conditions, and other patients requiring physical therapy during the outbreak.

Evidence from a study among 86,742 COVID-19 cases revealed an increase in rates of

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heart attack by nearly 5 times. In addition, the risk of a first stroke due to blockage of blood vessels increased three to six times which was sustained for at least 4 weeks [4].

Importantly, the study did not include people who had previously had a heart attack or stroke in the past, which may suggest that the risk of another heart attack or stroke in people who have had one may probably be even significantly higher.

COVID-19 affects the inner surfaces of the veins and arteries, causing inflammation of blood vessels (endothelium) followed by damage to very small vessels and culmination as blood clots, leading to disturbances in blood flow to the heart or blood clots in other parts of the body. This results in a stroke or heart attack.

Direct myocardial injury by viral involvement of cardiomyocytes, indirect and direct inflammatory damage, O_2 supply–demand imbalance, and increase of atherothrombotic events due to inflammatory destabilization of atheromatous plaques may result in myocardial infarction and/or heart failure [5–7].

Acute cerebrovascular disease, particularly ischemic stroke is caused by involvement of large vessel occlusion, multi-territory stroke, and otherwise uncommonly affected vessels. On the contrary, small-vessel brain disease, cerebral venous thrombosis, and intracerebral hemorrhage appear to be less frequent [8].

Hypertension seems to enhance the inflammatory profile in patients with SARS-CoV-2 infection [5], and hyperglycemia might modulate immune and inflammatory responses, thus predisposing patients to severe COVID-19 and possible lethal outcomes [9]. It is not a coincidence that hypertension (56.6%) and diabetes (33.8%) are the most prevalent comorbidities among individuals with COVID-19, who require hospitalization [5].

To date, effective therapies against COVID-19 are not currently available. All the governments have invested their efforts on vaccines, which are considered as the only effective weapons to curb the COVID-19 pandemic. However, the onset of new SARS-CoV-2 variants, the high vaccine hesitancy rates in rich countries, and the huge vaccination rate disparity between rich and poor countries are delaying the mass vaccination campaign worldwide.

Therefore, data on COVID-19-related myocardial infarction and ischemic stroke are worrying and indicate the need to implement prophylaxis in the form of anticoagulants, which could be used routinely in the event of thrombosis caused by COVID-19. For this reason, cardiological guidelines for the treatment of post-COVID-19 syndromes should also be established, to drive healthcare workers especially when high-risk categories such as older, obese and patients affected by comorbidities are affected by COVID-19 infection.

This could reduce the incidence and mortality associated with COVID-19-related acute myocardial injury or stroke, and prevent severe forms of COVID-19 infection associated with coagulation changes and the risk of thrombosis, particularly in the features of pulmonary embolism and acute respiratory distress syndrome.

Conflict of interest: None declared

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LETTER TO THE EDITOR

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Variant lambda of the severe acute respiratory syndrome coronavirus 2: A serious threat or the beginning of further dangerous mutations

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In mid-June, the World Health Organization (WHO) recognized the Lambda variant as a so-called Variants of Interest (VOI) [1]. In addition to Lambda, this list includes six others: Epsilon (B.1.427/B.1.429, formerly Californian), Iota (B.1.526, New York), and Theta (P.3, Filipino). This means that these variants have mutations that affect, inter alia, the ease of transmission of the pathogen, the severity of the disease, the ability to avoid vaccines, or misleading diagnostic tests. On the basis of genome sequencing, it was estimated that this variant contains 27 mutations (1 in ORF1a — deletion 3675-3677; 7 in the gene encoding protein S — deletion 246-252, G75V, T76I, L452Q, F490S, D614G and T859N as well as 19 other mutations which are observed in various known variants of the SARS-2 coronavirus). Among the Lambda variant mutations, the L452Q mutation was identified, which is similar to the L452R mutation observed in the Delta and Epsilon variants [2]. A new variant of interest in severe acute respiratory syndrome coronavirus 2 (SARS--CoV-2), designated Lambda, has spread in recent months in some South American countries, but its virological and evolutionary features remain unknown. The Lambda variant spike protein may increase viral infectivity, which is attributed to the mutations designated T76I and L452Q. The RSYLTPGD246-253N mutation, which is a unique 7-amino acid deletion in the N-terminal domain of the Lambda variant spike protein, avoids neutralizing antibodies. As the SARS-CoV-2 Lambda variant has spread dominantly in line with the increasing frequency of isolates carrying the RSYLTPGD246-253N mutation, these data suggest that the insertion of the RSYLTPGD246-253N mutation is closely related to the massive spread of Lambda variant infection in South America. Thus, the spike protein of the Lambda variant increases its infectivity, and the T76I and L452Q mutations are responsible for this property, and together with the RSYLTPGD246-253N and F490S mutation they confer resistance to antiviral antibodies [3]. The effect of such mutations on infectivity and immune escape from

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neutralizing antibodies is completely unknown to us. The studies showed an increased infectivity of the Lambda variant, which was even higher than that of D614G (a line of Alpha and Gamma variants). Compared to the wild type (line A), the neutralization was reduced 3.05-fold for the Lambda variant, while it was 2.33-fold for the Gamma variant and 2.03-fold for the Alpha variant. These results indicate that mutations present in the spike protein of the Lambda variant of interest result in increased infectivity and immune escape from neutralizing antibodies induced by an inactivated CoronaVac vaccine (not available in the European Union or the United States). These results show that in countries with high levels of SARS-CoV-2 infections, genetic surveillance should be associated with the identification of new isolates harboring mutations in the spike protein gene and immunological studies to determine the effect of these mutations on immune escape and breaking vaccine immunity [4]. Fortunately, the Lambda variant remains susceptible to neutralization by vaccine-induced mRNA antibodies. Lambda variant was more infectious and was neutralized by convalescent sera and vaccine-induced antibodies with a relatively small 2.3–3.3-fold decrease in titer, however this decrease was present. therefore, vaccination based on mRNA technology should be used universally and the whole world should focus on their universal use as well as on enabling their use in poorer countries [5]. According to Johns Hopkins Coronavirus Resource Center, Peru currently has the highest mortality rate, which is 600 deaths per 100,000 infected with COVID-19, in addition, the WHO reports that in Peru, the Lambda varianthas affected about 81% of patients since April, which additionally raises concern about the spread of this variant around the world [6].

We must pay special attention to the Lambda variant of the SARS-CoV-2 due to its possible escape from the surveillance of the host's immune response and possible ineffectiveness or limited effectiveness of preventive vaccinations. We should also consider a possible change in vaccination in countries such as Peru and the use of the most effective of them, such as those produced by Pfizer and Moderna, based on mRNA technology. Vaccinating the society as quickly as possible and with the most effective preparations should reduce the transmission of the virus and the risk of mutations that will no longer be resistant to the preventive measures we currently know. In the case of the Lambda variant, it is also necessary to consider the introduction of compulsory wearing of masks and travel restrictions, as well as implementing quarantine for returnees, regardless of vaccination status.

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LETTER TO THE EDITOR

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Myocarditis: A complication of COVID-19 and long-COVID-19 syndrome as a serious threat in modern cardiology

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Myocarditis is the inflammation of the heart muscle and is usually a consequence of a viral infection [1]. Because this disease can cause the destruction of myocytes, it may result in cardiomyopathy, heart failure, and sudden cardiac death. Cardiovascular complications from coronavirus disease 2019 (COVID-19) are emerging [2], especially during hospitalization, and myocarditis has been identified as a cause of death in some COVID-19 patients [3]. In the current epidemiological situation of a very large number of hospitalized patients, we must consider the long-term effects of myocarditis caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Initial reports based on magnetic resonance imaging studies showed 78% of patients with myocardial abnormalities and 60% with ongoing myocarditis 2 to 3 months after COVID-19 infection. High blood troponin concentrations were also found in 76% of patients, although their heart function was preserved [4]. In other studies, about 10 weeks after SARS-CoV-2 infection, 37% of patients were also diagnosed with myocarditis, despite only half of the respondents having symptoms of COVID-19 infection [5]. In contrast, the most recent reports that analyzed data for a fifth of the United States (US) population showed that males between 12 and 17 years of age most likely developed myocarditis within 3 months of SARS-CoV-2 infection, with an incidence of approximately 450 per million infections. The most recent CDC reports, indicating the number of infected teenagers in the US is the highest in all age groups, suggest that myocarditis will become a significant burden [6]. The reports also estimate a 16 times higher risk in patients with COVID-19 compared to the general population, with an incidence of COVID-19-associated myocarditis of approximately 150 cases per 100,000 [7].

In light of these numbers, cardiac complications both during and after the SARS-CoV-2 infec-

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tion will become a significant burden. Currently, the only effective method of preventing COVID-19 complications is vaccination, which reduces not only the risk of infection and mortality but also its long-term complications, i.e., long-COVID-19. In a study of 971,504 fully vaccinated people, only 0.2% developed COVID-19 symptoms, and only 31 developed long-COVID-19. On the other hand, the rate of COVID-19 infections was 11% in the unvaccinated group [8].

There is a lessor need to focus on myocarditis following mRNA vaccination [9]. This is because the infection and hospitalization rates are 17 times lower when compared to the unvaccinated group [10]. In summary, it is necessary to vaccinate the whole of society as soon as possible, perform further research on myocarditis in long-COVID-19 syndrome, create effective screening systems, and provide care for people suffering from long-COVID-19 syndrome before it leads to more serious complications.

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