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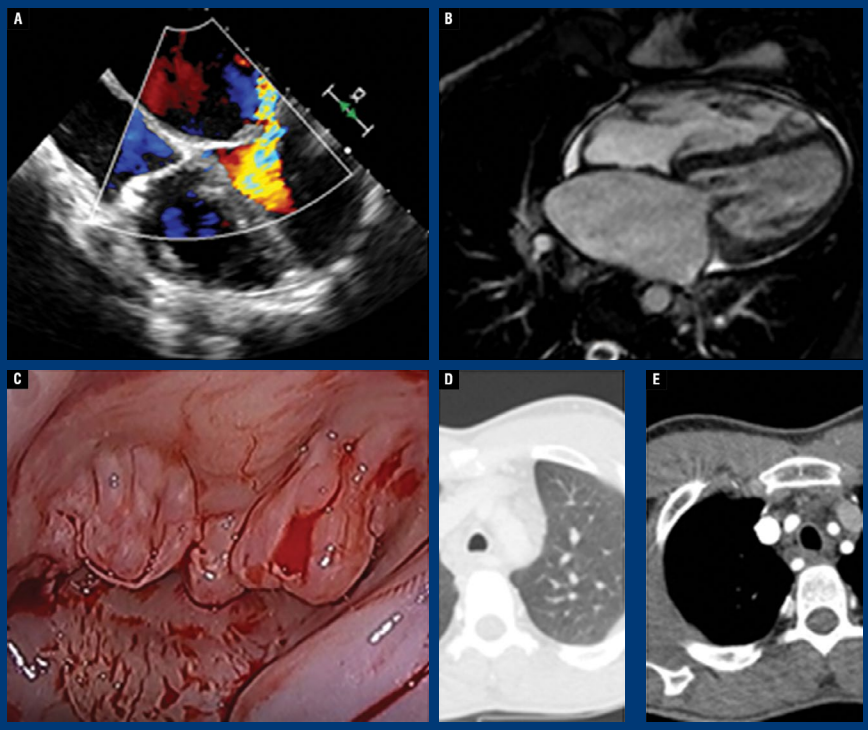

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EDITORIAL

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Opioids and oral P2Y12 receptor inhibitors: A drug–drug interaction

Jacek Kubica

Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland

As recommended in the European Society of Cardiology guidelines, titrated intravenous opioids should be considered to relieve pain in patients presenting with ST-segment elevation myocardial infarction (STEMI) (class of recommendation IIa, level of evidence C) [1]. The class of recommendation for morphine use in STEMI has been lowered from I to IIa (i.e., from "it is indicated" to "should be considered") as compared to previous guidelines, due to the unfavorable impact of morphine on P2Y12 receptor inhibitors bioavailability and their antiplatelet effect [2–4].

The CRUSADE registry was the first to suggest drug–drug interaction between morphine and a P2Y12 receptor inhibitor, as it reported an increased prevalence of adverse clinical outcome in acute coronary syndrome (ACS) patients receiving morphine and clopidogrel [5]. This suggestion was then proven in a randomized, placebo-controlled trial in patients with acute myocardial infarction (AMI) [2] and was confirmed in several other studies [3, 4, 6–8]. According to ticagrelor pharmacokinetic and pharmacodynamic studies, compared with healthy volunteers, patients with uncomplicated AMI appear to have similar plasma concentrations of ticagrelor and its active metabolite — AR-C124910XX after loading dose administration. Co-administration of morphine results in a decrease in ticagrelor bioavailability to a degree similar in both groups. However, while platelet inhibition in healthy volunteers is largely independent of morphine, in AMI patients the antiplatelet effect of ticagrelor is significantly less pronounced with co-administration of morphine [4, 9]. The greater susceptibility to the P2Y12 receptor inhibitor-morphine interaction seen in AMI patients is probably due to enhanced platelet activation in this subset of patients. In a meta-analysis by Gue et al. [10], patients pretreated with morphine were shown to have a higher rate of reinfarction than those not receiving morphine. Several approaches to overcome the "morphine effect" in patients with ACS have been proposed, showing some, but unsatisfactory effects [11–16]. Iglesias et al. [17] reported results of the PERSEUS study — a randomized trial comparing the impact of fentanyl versus morphine on ticagrelor pharmacokinetics and pharmacodynamics in STEMI patients undergoing primary percutaneous coronary intervention (PCI). Previously, reduced bioavailability of ticagrelor had been demonstrated when co-administered with fentanyl in stable patients [17], however the influence of fentanyl on ticagrelor absorption and platelet inhibition in AMI patients had not been established. The PERSEUS study was prematurely terminated after the inclusion of 68% of originally designed study population due to a slower than anticipated patient enrolment rate resulting in loss of statistical power. Nevertheless, the study brought consistent pharmacodynamic and pharmacokinetic evidence that fentanyl may be associated with a more favourable ticagrelor absorption profile

Address for correspondence: Prof. Jacek Kubica, Department of Cardiology and Internal Medicine, Collegium Medicum, Nicolaus Copernicus University, ul. M. Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland, e-mail: jkubica@cm.umk.pl

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than morphine, while exerting a similar analgesic effect. Indeed, these results do provide a strong premise supporting the preferential use of fentanyl over morphine in symptomatic STEMI patients undergoing primary PCI. The PERSEUS study, however, does not provide a comparison with any non-opioid treatment strategy, making it impossible to truly assess the effects of fentanyl on the pharmacokinetics and pharmacodynamics of ticagrelor in AMI patients. In this specific clinical setting, despite opioid-induced decreased bioavailability of P2Y12 receptor inhibitors, some additional factors, including enhanced platelet activation and reduced gastrointestinal perfusion as well as impact of mild therapeutic hypothermia applied in cardiac arrest survivors, may also impede the effect of oral antiplatelet drugs [18–24].

Further research enriches the knowledge on the possibility of reducing the clinical significance of the opioid-P2Y12 receptor inhibitor interactions, however, without bringing any breakthroughs to date. Therefore, for the time being, ensuring immediate inhibition of platelets by using the bridging therapy with cangrelor, seems to be the best solution of all [25, 26]. Nevertheless, the limited availability of this intravenous P2Y12 receptor inhibitor is a serious obstacle to widespread implementation of this approach.

Conflict of interest: None declared

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POSITION PAPER

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TIMES TO ACT. Italian-Spanish-Polish-Uzbek Expert Forum Position Paper 2022. Dyslipidemia and arterial hypertension: The two most important and modifiable risk factors in clinical practice

Krzysztof J. Filipiak[1], Miguel Camafort Babkowski[2], Matteo Cameli[3], Stefano Carugo[4, 5], Claudio Ferri[6], Djamshid B. Irisov[7], Krzysztof Narkiewicz[8], Ulugbek Nizamov[9], Leopoldo Pérez de Isla[10], Anna Tomaszuk-Kazberuk[11], Andrea Ungar[12], Aleksandra Gąsecka[13]

[1]Institute of Clinical Sciences, Maria Sklodowska-Curie Medical Academy, Warsaw, Poland; [2]Hypertension Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain; [3]Department of Medical Biotechnologies, Division of Cardiology, University of Siena, Siena, Italy; [4]Department of Clinical Sciences and Community Health, University of Milan, Milan, Italy; [5]Cardiology Unit, Department of Internal Medicine, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico of Milan, Milan, Italy; [6]University of L'Aquila, MeSVA Department and San Salvatore Hospital, UOC Internal Medicine and Nephrology, Hypertension and Cardiovascular Prevention Unit, L'Aquila, Italy; [7]Cardiac Arrhythmias Department, Republican Specialised Center of Cardiology, Tashkent, Uzbekistan; [8]Chair and Department of Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland; [9]Department of Ischemic Heart Disease and Atherosclerosis, Republican Specialised Center of Cardiology, Tashkent, Uzbekistan; [10]Department of Cardiology, Hospital Clínico San Carlos, Madrid, Spain; [11]Department of Cardiology, Medical University of Bialystok, Bialystok, Poland; [12]Geriatric and Intensive Care Medicine, Hypertension Center, University of Florence and Careggi Hospital, Florence, Italy; [13]1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

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Abstract

Hypertension and lipid disorders are two of the main cardiovascular risk factors. Both risk factors — if detected early enough — can be controlled and treated with modern, effective drugs, devoid of significant side effects, available in four countries as different as Italy, Spain, Poland, and Uzbekistan. The aim herein, was to develop this ***TIMES TO ACT*** *consensus to raise the awareness of the available options of the modern and intensified dyslipidemia and arterial hypertension treatments. The subsequent paragraphs involves consensus and discussion of the deleterious effects of COVID-19 in the cardiovascular field, the high prevalence of hypertension and lipid disorders in our countries and the most important reasons for poor control of these two factors. Subsequently proposed, are currently the most efficient and safe therapeutic options in treating dyslipidemia and arterial hypertension, focusing on the benefits of single-pill combination (SPCs) in both conditions. An accelerated algorithm is proposed to start the treatment with a PCSK9 inhibitor, if the target low-density-lipoprotein values have not been reached. As most patients with hypertension and lipid disorders present with multiple comorbidities, discussed are the possibilities of using new SPCs, combining modern drugs from different therapeutic groups, which mode of action does not confirm the "class effect". We believe our consensus strongly advocates the need to search for patients with cardiovascular risk factors and intensify their lipid-lowering and antihypertensive treatment based on SPCs will improve the control of these two basic cardiovascular risk factors in Italy, Spain, Poland and Uzbekistan.* (Cardiol J 2022; 29, 5: 730–738)

Key words: cardiovascular prevention, hypertension, hypercholesterolemia, single-pill combination (SPC)

Address for correspondence: Aleksandra Gąsecka, MD, PhD, 1st Chair and Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02–097 Warszawa, Poland, e-mail: aleksandra.gasecka@wum.edu.pl

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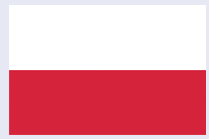
Introduction

Hypertension and lipid disorders, especially hypercholesterolemia (too high plasma low-density lipoprotein [LDL] concentration, which is the most atherogenic lipid fraction) are two of the main cardiovascular risk factors. Both risk factors — if detected early enough — can be controlled and treated with modern, effective drugs, devoid of significant side effects. All these drugs are currently available in the four countries mentioned, which are as different as Italy, Spain, Poland, and Uzbekistan. Table 1 presents a comparison of the epidemiological, population, wealth and medical care characteristics in these countries. Considering the high prevalence of cardiovascular risk factors in these countries and the deleterious effect of coronavirus disease 2019 (COVID-19) on the cardiovascular community, the aim was to develop the **TIMES TO ACT** consensus to raise the awareness of the available options of the modern and intensified dyslipidemia and arterial hypertension treatment. Below, in the subsequent paragraphs of the consensus, the treatment of dyslipidemia and arterial hypertension is discussed, focusing on the benefits of single-pill combination (SPC) approach in both conditions [1, 2].

TIMES TO ACT

The pandemic time has impacted all patients over the last 2 years. The COVID-19 pandemic

Table 1. Comparison of the epidemiological, population, wealth and medical care characteristics in countries of the authors of the presented Position Paper. Regarding the different methods of data collection and management in different countries, the presented data should be interpreted with caution.

Parameters	 Italy	 Spain	 Poland	 Uzbekistan
Population at the time of writing the Position Paper	60 million	47 million	38 million + 2 million immigrants from the Ukraine	33 million
Population density (inhabitants/km^2)	200	96	122	77
GDP per capita — recent data announced before the pandemic in 2019	36,957 USD	40,139 USD	31,939 USD	7665 USD
Elevated LDL cholesterol	20 million (33%)	7 million (15%)	19 million (48%)	17.5 million (53%)
Arterial hypertension	18 million (31%)	19 million (40%)	12 million (30%)	8.6 million (26%)
Active smoking	11 million (18%)	9 million (19%)	8 million (20%)	6.3 million (19%)
Obesity (BMI > 30 kg/m^2)	10 million (17%)	8 million (17%)	7 million (18%)	6.2 million (18%)
Chronic kidney disease (eGFR < 60 mL/min/1.73 m^2)	4 million (7%)	8 million (17%)	4.5 million (11%)	3.1 million (9%)
Diabetes mellitus	3.5 million (6%)	4 million (9%)	3 million (8%)	5.2 million (16%)
Heart failure with reduced ejection fraction	1.2 million (2%)	1.2 million (2.5%)	1.2 million (3%)	0.9 million (2.7%)
Number of doctors per 10,000 inhabitants	40	53	24	26
Number of cardiologists per million inhabitants	300	50	100	30
Number of internists per million inhabitants	480	228	480	182
Number of family doctors/ /general practitioners per million inhabitants	600	770	580	686

BMI — body mass index; GDP — gross domestic product; eGFR — estimated glomerular filtration rate; LDL — low-density lipoprotein

was associated not only with a significant number of deaths due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections and collateral deaths resulting from the failure of the health care system, but has also drawn attention to the need for good control of cardiovascular risk factors, with multiple measures undertaken to improve prognosis, especially in patients at high cardiovascular risk [3–6]. It is people with cardiovascular risk factors who died more often and experienced the severe course of COVID-19 more often [4, 7, 8]. The literature frequently refers to syndemics — diseases accompanying the pandemic, in which the deterioration of care, as well as particularly high mortality in the case of SARS-CoV-2 virus infections were observed [9, 10]. Syndemics includes: arterial hypertension, hypercholesterolemia, diabetes, obesity or heart failure [11, 12]. All of these conditions increased the risk of death due to COVID-19 [13]. At the same time, the pandemic itself was associated with less frequent detection of arterial hypertension, less frequent laboratory tests in the field of lipid disorders, generating the so-called health debt in many countries [14]. Therefore, there is a need to make up for this debt and to intensify the treatment of hypertension and lipid disorders in all our countries [15].

Irrespective of which country was analyzed, in each of the countries, the percentage of patients with hypertension ranges from 26% to 40% and patients with hypercholesterolemia — from 15% to 53%. In total, in four of these countries it was estimated that 17–32% of patients were obese, 18–21% smoked cigarettes, 6–15% had diabetes, 7–17% suffered from chronic kidney disease, and at least 1–3% had heart failure [16–18]. When analyzing medical care that targets the most important cardiovascular risk factors, the biggest problem is the relatively small number of cardiologists per 10,000 inhabitants in Uzbekistan, there were a small number of all medical doctors in Poland and Uzbekistan, a high prevalence of obesity and diabetes in Uzbekistan, a high prevalence of chronic kidney disease in Spain and too many active smokers in all the countries [19–21].

Cardiovascular risk factors closely coexist, but hypertension and hypercholesterolemia are undoubtedly the easiest to control with the use of adequately selected, modern drugs, which are well-tolerated by patients. The most important reasons for poor control of these two factors on a population scale remain unchanged and mainly include:

— Insufficient awareness and diagnostics of these diseases [22–24];
— No treatment, even after setting the diagnosis [25–27];
— Low adherence and persistence to chronic long-term treatment [28–32];
— Lack of properly selected and, if necessary, increasing intensity of pharmacotherapy (therapeutic inertia) — using too low doses of medications [33–35];
— Lack of consciousness that the medications should be administered for the rest of patients' life [36–38];
— Failure to use the most modern pharmacological options which are very effective and safe, and instead — continuation of therapy using medications from older generations, with lower efficacy [39–41];
— The lower target levels of these risk factors recommended in the recent years, especially with regard to LDL-cholesterol, with the target levels < 55 mg/dL (< 1.4 mmol/L), along with a reduction of at least 50% from the initial value in patients at very high cardiovascular risk, and < 70 mg/dL (< 1.8 mmol/L) in patients at high cardiovascular risk [42, 43].

Monotherapy seems to still be a very important step in hypercholesteremia treatment. Therefore, it is so crucial to choose the right statin to start the LDL-cholesterol lowering therapy. Statins reduce cholesterol synthesis in the liver by competitively inhibiting the activity of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA, hydroxy-methylglutaryl coenzyme A) reductase. They belong to the most extensively-studied drugs in the prevention of cardiovascular diseases, and their effect on the reduction of cardiovascular deaths has been demonstrated in many clinical studies. The most effective statin to reduce the LDL-cholesterol level available today is rosuvastatin [44]. Even in the apparently statin-intolerant patients, re-starting lipid-lowering treatment with low-dose rosuvastatin is a reasonable option [45].

Regarding the lipid-lowering potency, the lowest recommended dose of rosuvastatin, 5–10 mg, is equivalent to 20–30 mg atorvastatin. This means that the conversion of the lipid-lowering effectiveness of rosuvastatin to atorvastatin corresponds more to a ratio of 1:3 rather than 1:2. Therefore, the availability of the 15 mg and 30 mg doses of rosuvastatin in some countries increases the applicability of rosuvastatin to patients who are already taking 40 mg and 80 mg of atorvastatin, respectively. Atorvastatin undergoes biotransformation in the liver via the CYP450 3A4 system, while rosuvastatin is metabolized by the liver only to a minor

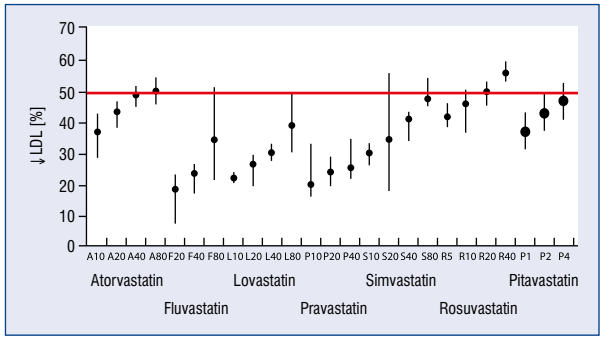


Figure 1. Comparison of lipid-lowering efficacy of the currently available statins in different doses. The horizontal line shows the 50% low-density lipoprotein (LDL) reduction, required by the latest European guidelines for the treatment of hypercholesterolemia in all patients at high and very high cardiovascular risk (adapted from: [45, 47]).

extent, interacting with the CYP2C9 isoenzyme and to a much lesser extent with CYP3A4. These differences are important because of the potential for drug interactions, which are very rare with rosuvastatin. Rosuvastatin doses of 40 mg/24 h provide the greatest confidence in reducing the baseline LDL-cholesterol by at least 50%, which is required by the latest European guidelines for the treatment of hypercholesterolemia in all patients at high and very high cardiovascular risk (Fig. 1) [46, 47].

Ezetimibe is an essential companion for statin, preferably rosuvastatin to maximize the lipid-lowering effect nowadays [48]. It is estimated that only few percent of patients in the studied countries achieve the currently recommended target levels of LDL-cholesterol, and the reasons for this therapeutic failure are mainly:

— Lack of determination of doctors to use the strongest statins in the maximum tolerated doses (therapeutic inertia);
— Patients' reluctance and fear of using statins and disinformation by the so-called anti-statin movements, especially active in social media ("nocebo" phenomenon);
— A real intolerance of high doses of statins in some patients, mainly in the form of myalgia;
— Too infrequent use of combination therapy, based on the use of several lipid-lowering drugs with different mechanisms of action, which allow using the maximal tolerated doses of statins, while maintaining the therapeutic efficacy.

The above-mentioned reasons make it reasonable to recommend SPC, a single pill containing at least two substances, as the next step in pharmacotherapy — combinations containing statin and ezetimibe — a drug that reduces the absorption of cholesterol from the intestine.

The current European recommendations are based on models suggesting starting the therapy with a statin, adding ezetimibe after a few weeks (another oral drug with a different mechanism of action), and if it does not work — introducing additional injections of a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (Fig. 2) or inclisiran, introduced recently in some countries [49, 50].

In the current situation, in the post-COVID-19 era, it is often not possible to wait a few weeks to reach the target LDL level due to the difficulties in contacting the treating physician or a generated "health debt" in the system. It is also not reasonable to start the treatment with even the highest dose of a statin, if it is clear that it will not achieve the LDL target level anyway. In such cases, particularly in patients who require more than 50% LDL-cholesterol reduction, we propose the second model (Fig. 3) — to accelerate the algorithm — administer a statin with ezetimibe immediately and control the LDL cholesterol level a few weeks later to assess whether the addition of PCSK9 inhibitor is required [51, 52].

Statin choice with specific rosuvastatin increasing rapidly in many countries has also some pharmacological background reasons. As rosuvastatin has a lower risk of drug interactions, it has recently become a combination substance in SPC formulas, not only with ezetimibe [45]. An SPC combining rosuvastatin and an antiplatelet drug in one tablet (acetylsalicylic acid), recommended especially in the secondary prevention, may substantially simplify the therapy of many patients who have indications for both acetylsalicylic acid and a statin therapy [53]. On the other hand, the combination of rosuvastatin with the most popular and most extensively studied calcium antagonist (rosuvastatin/amlodipine) is an example of a hybrid, two-component SPC that simultaneously treats hypertension and hypercholesterolemia [54].

Treatment of arterial hypertension differs among many countries, but the principles and groups of antihypertensive drugs are common and widely recognized by International, American, European and national hypertension societies guidelines [55]. It has been proven many times that countries where an exceptionally high percentage of SPC preparations are used — such as Portugal or Spain — achieve better population

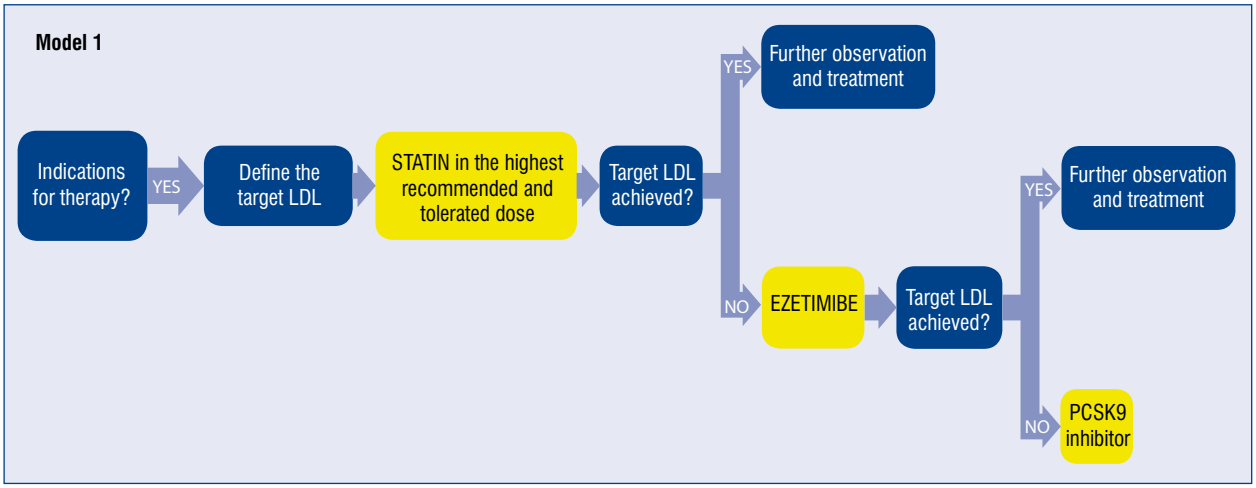


Figure 2. First model: the three-step algorithm for the treatment of hypercholesterolemia promoted in Europe from 2019; mandatory from 2020 (date of guidelines publication), developed by the European Society of Cardiology (adapted from: [48], modified); Y (yes) — goal achieved; N (no) — goal not achieved; LDL — low-density lipoprotein; PCSK9 — proprotein convertase subtilisin/kexin type 9.

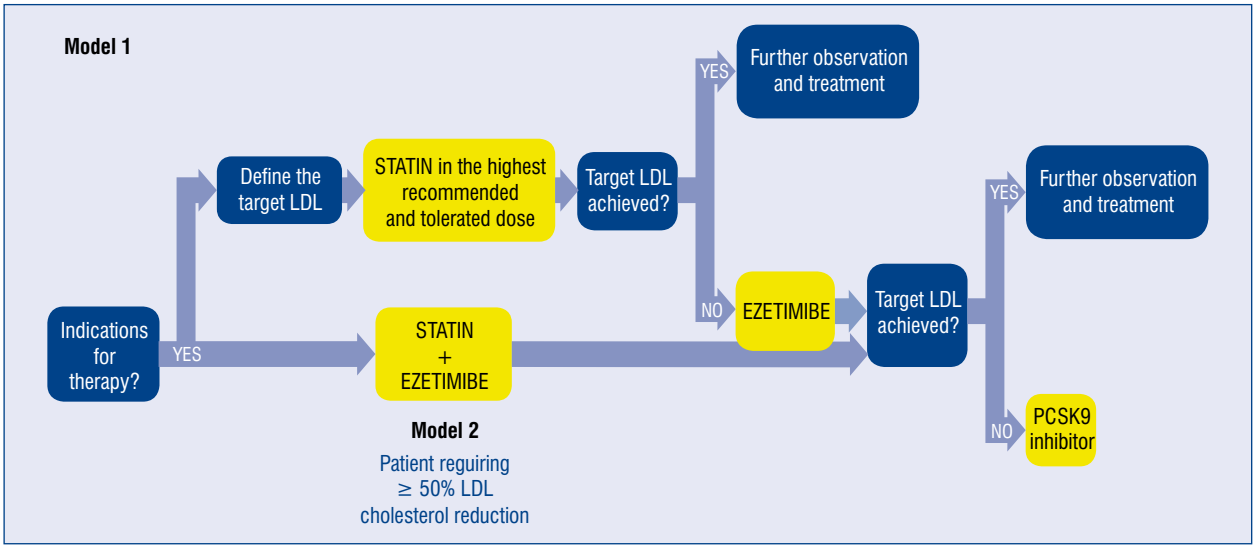


Figure 3. Second model. Accelerated algorithm to start the potential treatment with a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor (adapted from: [48], modified); LDL — low-density lipoprotein.

blood pressure control. The European guidelines from 2018 recommend the use of SPC as the first step of antihypertensive treatment [56]. An SPC should consist of an angiotensin converting enzyme (ACE) inhibitor or an angiotensin II receptor antagonist (ARB), in combination with a calcium channel blocker or a diuretic. Already in the second step of treatment, the combination of a drug that inhibits the renin–angiotensin system with a calcium antagonist and a diuretic in SPC can be used. A summary of this algorithm is shown in Figure 4. Hence, it is so important to be able to use the combined SPC of the most popular ACE inhibitors or ARB with a calcium channel blocker and/or a diuretic [57, 58].

One pill to treat arterial hypertension in SPC formula is becoming more and more popular [59, 60]. As a rule, SPC are available in several potencies, so the doses of drugs within a single SPC can be tailored to the individual needs of a patient [61–63].

For example, ramipril is one of the most commonly used ACE inhibitors in Europe and in the

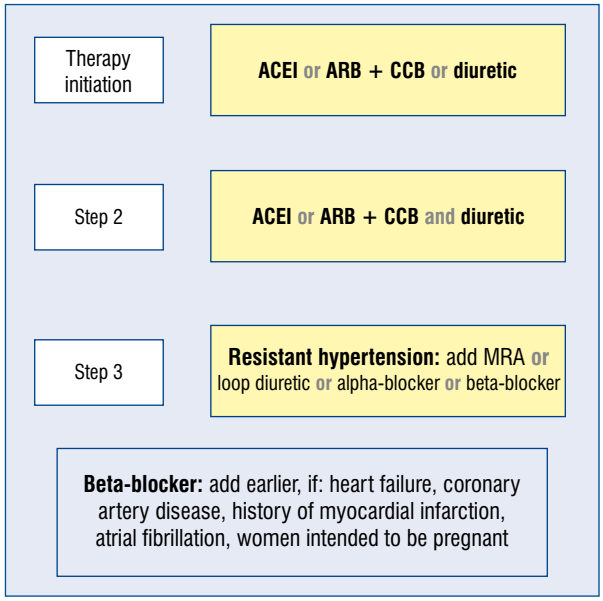


Figure 4. Algorithm to initiate antihypertensive therapy in most patients with arterial hypertension, as recommended in the 2018 guidelines of the European Society of Cardiology (adapted from: [56], modified); ACEI — angiotensin converting enzyme inhibitor; ARB — angiotensin II receptor antagonist; CCB — calcium channel blocker; MRA — mineralcorticoid receptor antagonist.

world, and the availability of its combinations with a diuretic, a calcium channel blocker (amlodipine), and as a triple combination (ramipril/amlodipine/ /hydrochlorothiazide) allows the continuation of antihypertensive treatment at various stages, intensification of treatment, if necessary, and enables the therapy with substances belonging to the most--extensively studied cardiological drugs [64, 65].

Regarding the ARB group, the most frequently selected drugs are those which ensure the 24-h blood pressure control, and which were showed to have the highest treatment efficacy in head-to--head studies against other drugs. According to the Experts of this Position Paper, the long-acting ARB like candesartan, olmesartan and telmisartan might be considered in the first place. In the case of their use, clinicians should be able to use SPC combining them with a calcium antagonist or a diuretic.

In the next stage of treatment, the availability of the three-component SPCs, such as candesartan/ /amlodipine/hydrochlorothiazide, olmesartan/amlodipine/hydrochlorothiazide, telmisartan/amlodipine/hydrochlorothiazide might further facilitate the control of the difficult to manage hypertension.

Additional SPC combinations are needed for some subsets of patients. For some patients, SPCs combinations other than those listed in the general arterial hypertension algorithm are particularly useful in clinical practice. A large group of patients in the secondary prevention of cardiovascular events requires the simultaneous administration of an ACE inhibitor and highly cardioselective beta--blocker. In this subgroup, SPC combining the most commonly used drugs in this group — bisoprolol and ramipril in one pill is of particular importance. Large groups of patients with chronic coronary syndromes, acute coronary syndromes, heart failure or atrial fibrillation are also typical patients who might benefit from such SPC. In some patients, an SPCs combining a beta-blocker and a calcium antagonist and a calcium antagonist with a diuretic may also be considered in some patients.

Comorbidities will be the essential factor for optimal treatment of arterial hypertension and hypercholesterolemia, as they contribute to the whole-panel risk factors of the patient. Therefore, it is so important for the patients who are the target population of this Position Paper to take care of weight reduction, smoking, adequate diabetes control, physical activity, salt restriction, healthy diet, inhibition of the chronic kidney disease and prevention of heart failure. To achieve this goal, regulation follow-up visits where compliance will be assessed are crucial. New therapies recently introduced in Europe (sodium-glucose co-transporter-2 [SGLT2] inhibitors — flozins or glucagon-like peptide 1 agonists) may help to tackle many of the above-mentioned health challenges and can be compared with statins regarding their wide-range action. New SPCs based on SGLT2 inhibitors are also expected to be introduced to the market in the future. Before our eyes, an epochal change in the treatment of diabetes is taking place, with the shift from sulfonylurea derivatives to the newest drugs: SGLT2 inhibitors, glucagon-like peptide 1 analogues.

Furthermore, there are many implications of wider possibilities of using new, modern drugs within the individual therapeutic groups, which mode of action does not confirm the "class effect". In this context, the following molecules might be particularly preferable as SPC combinations in the future:

- Eplerenone, and in the future finerenone over spironolactone [66];
- Torasemide over furosemide [67];
- Ranolazine over trimetazidine [68];
- Nebivolol over older beta-blockers [69].

Times to act is the title of our Position Paper. We believe that in post-COVID times, the need to

intensify treatment, to actively search for patients with cardiovascular risk factors, especially with hypercholesterolemia and arterial hypertension, should go hand in hand with the implementation of the latest therapy based on SPC with well-established, effective lipid-lowering and antihypertensive molecules, many of which are mentioned in our document [70]. This approach will enable even better control of these two basic cardiovascular risk factors in Italy, Spain, Poland and Uzbekistan.

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Ion channel inhibition with amiodarone or verapamil in symptomatic hospitalized nonintensive-care COVID-19 patients: The RECOVERY-SIRIO randomized trial

Eliano P. Navarese[1, 2, 3], Przemysław Podhajski[1], Felicita Andreotti[4, 5], Giuseppe La Torre[6], Robert Gajda[7], Adrian Radziwanowski[1], Małgorzata Nowicka[1], Paweł Bukowski[7], Jacek Gajda[7], Maciej Omyła[7], Piotr Lackowski[1], Maciej Piasecki[1], Małgorzata Jasiewicz[1], Paweł Szymański[8], Łukasz Pietrzykowski[1], Piotr Michalski[1], Aldona Kubica[9], Iwona Urbanowicz[1], Nicola Orsini[10], Max Conte[11], Jarosław Pinkas[12], Marc A. Brouwer[13], Jacek Kubica[1]

[1]Interventional Cardiology and Cardiovascular Medicine Research, Department of Cardiology and Internal Medicine, Nicolaus Copernicus University, Bydgoszcz, Poland
[2]Faculty of Medicine, University of Alberta, Edmonton, Canada
[3]SIRIO MEDICINE Research Network, Poland
[4]Fondazione Policlinico Universitario Gemelli IRCCS, Rome, Italy
[5]Catholic University Medical School, Rome, Italy
[6]Department of Public Health and Infectious Diseases, Sapienza University of Rome, Italy
[7]Department of Infectious Diseases, District Hospital, Pultusk, Poland
[8]Department of Infectious Diseases, Regional Hospital, Grudziadz, Poland
[9]Department of Health Promotion, Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz, Poland
[10]Department of Global Public Health, Karolinska Institutet, Stockholm, Sweden
[11]Anesthesia and Intensive Care Unit, Ospedale Bari Sud Di Venere, Bari, Italy
[12]Center of Postgraduate Medical Education, School of Public Health, Warsaw, Poland
[13]Department of Cardiology, Radboud University Medical Center, Nijmegen, the Netherlands

Abstract

Background: *Ion channel inhibition may offer protection against coronavirus disease 2019 (COVID-19). Inflammation and reduced platelet count occur during COVID-19 but precise quantification of risk thresholds is unclear. The RECOVERY-SIRIO study aimed to assess clinical effects of amiodarone and verapamil and to relate patient phenotypes to outcomes.*

Methods: *RECOVERY-SIRIO is a multicenter open-label 1:1:1 investigator-initiated randomized trial with blinded event adjudication. A sample of 804 symptomatic hospitalized nonintensive-care COVID-19 patients, follow-up for 28 days was initially planned.*

Results: *The trial was stopped when a total of 215 patients had been randomized to amiodarone (n = 71), verapamil (n = 72) or standard care alone (n = 72). At 15 days, the hazard ratio (hazard ratio [HR], 95% confidence interval [CI]) for clinical improvement was 0.77 (0.52–1.14) with amiodarone and 0.97 (0.81–1.17) with verapamil as compared to usual care. Clinically relevant associations were found*

Address for correspondence: Prof. Eliano P. Navarese, MD, PhD, FACC, FESC, Interventional Cardiology and Cardiovascular Medicine Research, Department of Cardiology and Internal Medicine, Nicolaus Copernicus University, ul. M. Skłodowskiej-Curie 9, 85–094 Bydgoszcz, Poland, tel: +48 52 585 4023, fax: +48 52 585 4024, e-mail: elianonavarese@gmail.com; eliano.navarese@cm.umk.pl

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between mortality or lack of clinical improvement and higher peak C-reactive protein (CRP) levels or nadir platelet count at 7, 10 and 15 days. Mortality rate increased by 73% every 5 mg/dL increment in peak CRP (HR 1.73, 95% CI 1.27–2.37) and was two-fold higher for every decrement of 100 units in nadir platelet count (HR 2.19, 95% CI 1.37–3.51). By cluster analysis, thresholds of 5 mg/dL for peak CRP and 187 × 10^3/mcL for nadir platelet count identified the phenogroup at greatest risk of dying.

Conclusions: *In this randomized trial, neither amiodarone nor verapamil were found to significantly accelerate short-term clinical improvement. Peak CRP and nadir platelet counts were associated with increased mortality both in isolation and by cluster analysis.* (Cardiol J 2022; 29, 5: 739–750)

Key words: amiodarone, verapamil, COVID-19, ion-channel inhibition, randomized trial

Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is characterized by viral entry and replication within host cells that may lead to full-blown 2019-coronavirus disease (COVID-19). The SARS-CoV-2 spike protein mediates virus entry through receptor binding and membrane fusion. Ions promote viral membrane fusion and conformational changes and allow fusion peptide insertion into the lipid bilayer followed by endocytosis [1, 2]. Interaction of viral proteins with host cell ion channel activity may represent a crucial virus–host mechanism [3]. Pharmacological agents targeting ion channels may modulate SARS-CoV2's life cycle [3]. Preliminary reports have shown potential antiviral efficacy of ion channel inhibitors in COVID-19 [4, 5].

Two cardioprotective agents, amiodarone and verapamil, are ion channel antagonists. This multicenter randomized study in symptomatic hospitalized nonintensive-care COVID-19 patients was conducted to compare the effects of amiodarone or verapamil on top of usual care versus usual care alone on progression of clinical status.

Enhanced inflammation and reduced platelet count caused presumably by platelet consumption are reported during COVID-19 in association with adverse prognosis [6, 7]. Within this randomized trial, the relation between biomarkers and outcomes were quantitatively addressed following prespecified analyses of biomarkers both in isolation and by cluster analysis; cluster analysis is a machine learning method allowing identification of distinct COVID-19 phenotypic groups.

Methods

Trial design and patient population

RECOVERY-SIRIO (ClinicalTrials.gov number NCT04351763) is a multicenter, investigator-initiated, not-for-profit, open-label randomized trial with clinical events validated by an independent clinical events committee that was unaware of treatment allocation. Eligible patients were randomly assigned in a 1:1:1 ratio to receive either amiodarone + usual care, verapamil + usual care or usual care alone, and were followed for up to 28 days. The study was approved by an independent Ethical Committee of the Nicolaus Copernicus University of Poland. Written informed consent was obtained from all patients. Full rationale of the study was previously presented [3]. Briefly, viral proteins interact with host cell ion channel activity [3, 4]. In the "early entry" phase, the viral S protein-subunit S1 binds the angiotensin converting enzyme 2 (ACE2)-receptor on human cells, with transmembrane protease-serine 2 (TMPRSS2) facilitating virus-membrane fusion [1]. Ca2+ ions promote viral membrane fusion and S protein conformational changes which allow insertion of the fusion peptide into the lipid bilayer. In the "late entry" phase, SARS-CoV-2 is endocytosed and Ca2+ ions have a role in endocytic vesicle maturation [8]. This process ends with the release of the viral genome into the cytoplasm and subsequent viral replication. Amiodarone and verapamil block Ca2+ channels in the cell membrane and endosomal/lysosomal membranes, thereby potentially interfering with the coronavirus' life-cycle [3, 8]. Experimental studies indicate that amiodarone impairs endosomal transport in SARS-CoV-2-infected cells by blocking ion channels [9].

The study was additionally conceived to identify, through serial laboratory measurements, parameters quantitatively predicting disease progression and mortality in hospitalized non-intensive care COVID-19 patients. The full trial protocol is detailed in **Supplement material.** The authors take full responsibility for the design and conduct of the trial and vouch for the accuracy and completeness of the data, data analysis, and protocol adherence.

No other author contributed to the writing of the manuscript apart from those listed herein.

Patient enrollment was conducted between May 20, 2020 and May 13, 2021. The main patient inclusion criteria were: 1) Confirmed COVID-19 based on real-time polymerase chain reaction of naso- or oropharyngeal swabs, sputum or tracheal aspirates; 2) Symptomatic hospitalization initially not requiring intensive care; 3) Age >18 years; 4) Oxygenation index — defined as the quotient of arterial oxygen partial pressure (PaO2 in mmHg) to fraction of inspired oxygen (FiO2) — > 200; 5) Written informed consent was given prior to any trial-related procedure. The trial conduction followed local regulations, the Declaration of Helsinki, and the guidelines for Good Clinical Practice by the International Council for Harmonisation Committee for Medicinal Products for Human Use (GCP CHMP/ICH/135/95).

Endpoints

Clinical outcomes

The primary study endpoint was the first change in at least one category toward clinical improvement from enrollment (i.e., baseline) up to 15 days. Clinical categories were defined as per World Health Organization (WHO) classification used in COVID-19 trials [10]. An ordinal scale from 1 to 7 was used to define categories: 1) Death; 2) Hospitalized patients requiring mechanical ventilation, extracorporeal membrane oxygenation (ECMO) or both; 3) Hospitalized patients requiring high flow nasal oxygen therapy, noninvasive mechanical ventilation or both; 4) Hospitalized patients requiring oxygen therapy; 5) Hospitalized patients not requiring oxygen therapy; 6) Nonhospitalized patients, but unable to resume normal activities; 7) Nonhospitalized patients with resumption of normal activities. Improvement was considered as the increase of at least one point on the ordinal scale, lower scores indicating worse outcomes and higher scores more favorable ones. Main secondary endpoints included clinical category improvement at 28 days, 28-day mortality, days of hospitalization and of oxygen therapy, mechanical ventilation, and 15-day National Early Warning Score 2 (NEWS2) values [11, 12].

Biomarkers

Serum C-reactive protein (CRP, mg/dL) and high-sensitivity (hs) cardiac troponin (cTn, ng/mL) I, whole blood platelet count (per mcL) and plasma D-dimers (ng/mL) were measured at prespecified time points (baseline, 7, 10 and 15 days) using Siemens Healthineers, Germany, for CRP and hs-cTn I, and routine chemical hematology for platelets and D-dimers. The coefficient of variation was < 10% for all measures. Prespecified peak or nadir values were analyzed.

Interventions

Allocation to amiodarone, verapamil or usual care alone was performed after patient enrollment by investigator connection to a prespecified web-link. The random allocation sequence was generated by computer software. During hospitalization patients randomized to amiodarone received usual care plus 200 to 400 mg of amiodarone daily (oral administration) adjusting to age, heart rate, blood pressure, QT/QTc interval and heart rhythm. Patients randomized to verapamil received usual care plus 120 to 480 mg of verapamil administrated orally in 3 to 4 divided doses every 6–8 hours (adjusted to age, heart rate, blood pressure, QT/QTc interval and heart rhythm). Patients randomized to usual care received no additional treatment (control group). Further drug administration details are provided in the full study protocol (**Supplement material**).

Statistical analysis

Power calculation for the primary efficacy endpoint was based on the assumption of superior clinical improvement at 15 days in favor of amiodarone plus usual care or verapamil plus usual care versus usual care alone. On the basis of preliminary data [3–5, 10] we assumed clinical improvement would occur in 30% of the control group [10] and in 39% of the experimental group (amiodarone or verapamil) [3–5], resulting in an overall sample size of 804 subjects to achieve at least 80% power at a 0.05 significance level.

The primary efficacy analysis was on an intention-to-treat basis. Hazard point estimates with two-sided 95% confidence interval (CI) measured by the hazard ratio (HR) were calculated based on the Cox proportional hazards model. Probability of clinical improvement is presented using the Kaplan–Meier curves. Data distribution was checked by the Kolmogorov-Smirnov test with data presented as median with interquartile range (IQR) or mean ± standard deviation (SD) as appropriate. Baseline characteristics were compared by χ^2 or the Fisher exact test for categorical variables and by the Kruskal-Wallis, t-test or ANOVA for continuous variables. To determine independent predictors of mortality, the following routine laboratory values were prespecified, based on

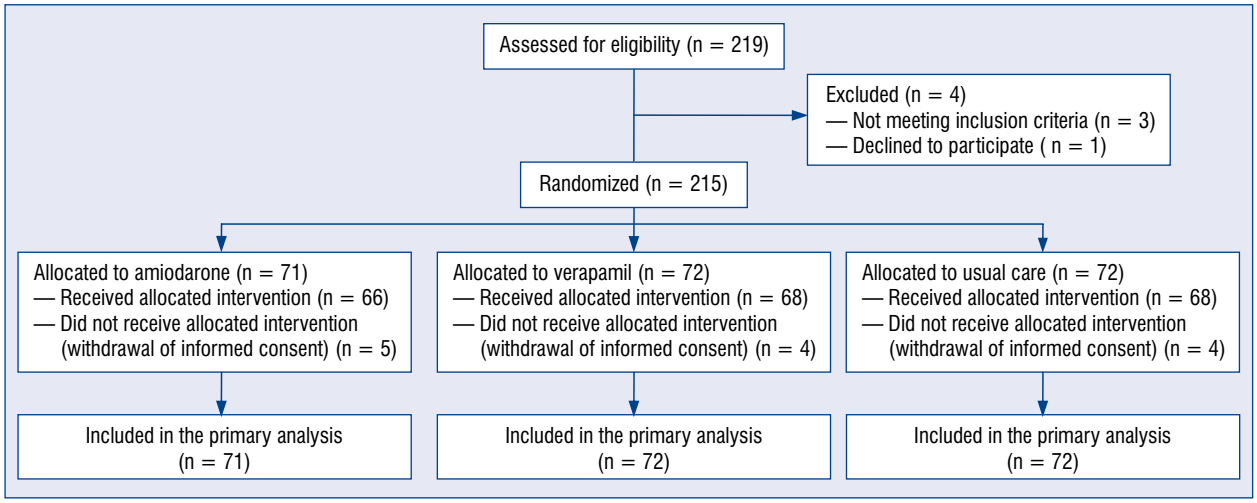

Figure 1. Randomization and treatment assignment.

their known clinical relevance in COVID-19: peak values of CRP, D-dimers, hs-cTn I and total white blood cell count, as well as nadir values of platelet and lymphocyte counts [6, 7]. Visual associations between continuous biomarkers and mortality were evaluated by restricted cubic splines with 3 knots at fixed percentiles in Cox regression models. A Wald-type test was applied to test for non-linearity of the models.

An unsupervised cluster analysis was conducted using a machine learning method that allows categorization of complex entities by segregating samples into homogenous groups based on each cluster's dissimilarities. For cluster analysis, the partitioning around medoids (PAM) algorithm was applied, which is less sensitive to outliers and more robust compared to k-means [13]. The number of clusters was selected on the basis of minimal total intra-cluster variation or minimal total within-cluster sum of squares (WSS). Total WSS measures the compactness of clustering. After allocating each patient to a cluster, cluster phenotypes and outcomes were compared by the Kaplan–Meier curves. A two-tailed p-value < 0.05 was considered statistically significant.

Results

Patient enrollment and characteristics

Enrollment began in May 2020. Owing to a slower than predicted recruitment caused by abatement of new COVID-19 cases in Poland in the second half of 2021, the trial was terminated prematurely by the Steering Committee at the prespecified interim analysis of May 2021 with a final sample size of 215 subjects. The CONSORT flow diagram of patient disposition through the study is illustrated in Figure 1: 71 patients were assigned to receive amiodarone (93% or 66 actually received the drug), 72 to verapamil (94% or 68 actually received the drug) and 72 to standard care alone. None of the patients were admitted to an intensive care unit at the time of enrollment.

Baseline characteristics (Table 1) were balanced among amiodarone, verapamil and control groups in terms of age (median 60, 62 and 63 years, respectively) and sex (69%, 58% and 64% men, respectively). Underlying cardiovascular disease was present in 35%, 40% and 33% ($p = 0.66$), and diabetes mellitus in 23%, 25% and 24%, respectively ($p = 0.94$). Median days from symptom onset to randomization were 7 (4–8) for amiodarone, 6 (3–8) for verapamil and 6 (4–9) for usual care ($p = 0.49$). At enrollment no significant intergroup differences emerged in other demographic or laboratory characteristics, clinical category ordinal scale or NEWS2 values (Table 1). During the trial, therapeutic measures against COVID-19 and its sequelae (including chloroquine, azithromycin, convalescent plasma, heparin and acetylsalicylic acid) were administered in a balanced way to the three treatment groups (Table 1).

Primary and secondary endpoints

Clinical outcomes

The rate of clinical category improvement at 15 days did not differ significantly among arms: it occurred in 56.3% with amiodarone, 68.1% with verapamil and 68.1% with usual care (Table 2). At 15 days the HRs (95% CI) for clinical improvement

Table 1. Baseline characteristics of the three randomized groups.

	Amiodarone (n = 71)	Verapamil (n = 72)	Usual care alone (n = 72)	P
Median age [years]	60 (51.5, 71)	62 (50.75, 72.25)	62.5 (52, 72)	0.58
Male sex	49 (69%)	42 (58%)	46 (64%)	0.41
Cardiovascular disease	25 (35%)	29 (40%)	24 (33%)	0.66
Diabetes	16 (23%)	18 (25%)	17 (24%)	0.94
Cancer	7 (10%)	5 (7%)	3 (4%)	0.37
COPD	4 (6%)	5 (7%)	5 (7%)	1
Median body mass index [kg/m^2]	28.25 (25.85, 32.94)	30.45 (27, 32.8)	29.36 (26.74, 32.32)	0.32
Median days from illness onset to randomization	7 (4, 8)	6 (4, 9)	6 (3, 8)	0.494
PO2/FiO2	324.10 ± 98.48	317.76 ± 94.90	325.69 ± 92.60	0.87
Requiring O2 therapy	49 (69%)	52 (72%)	49 (68%)	0.85
Cough	45 (63%)	45 (62%)	46 (64%)	0.98
Dyspnea	53 (75%)	48 (67%)	44 (61%)	0.22
Muscle or joint pain	19 (27%)	10 (14%)	17 (24%)	0.14
Diarrhea	21 (30%)	12 (17%)	14 (19%)	0.14
Fatigue	59 (83%)	54 (75%)	62 (86%)	0.20
Chest pain	11 (15%)	11 (15%)	19 (26%)	0.15
Fever	55 (77%)	50 (69%)	54 (75%)	0.53
Median body temperature [°C]	36.7 (36.6, 36.95)	36.7 (36.5, 37.23)	36.8 (36.6, 37.5)	0.39
Median pulse rate [bpm]	81 (73, 92.5)	85.5 (76.75, 96)	84 (76, 92.25)	0.31
Respiratory rate [/min]	16.46 ± 2.56	16.50 ± 2.32	16.53 ± 2.33	0.98
Median NEWS2	3 (2, 4)	2 (2, 4)	3 (2, 4)	0.80
Platelet count [10^3/mcL]	182.48 ± 2.17	210.70 ± 87.36	200.77 ± 92.29	0.13
WBC count [×10^3/mcL]	5.96 ± 2.23	6.50 ± 3.13	6.16 ± 2.36	0.45
Median lymphocytes count [×10^3/mcL]	0.96 (0.73, 1.42)	1.04 (0.8, 1.5)	1 (0.65, 1.39)	0.86
Serum creatinine [mg/dL]	0.95 ± 0.30	1.02 ± 0.99	1.03 ± 1.15	0.82
Median ALT [mg/dL]	29.32 (22.85, 44.89)	31.64 (20.94, 51.31)	28.09 (20.09, 54.5)	0.97
Median D-dimer [ng/mL]	500.16 (398.48, 989.51)	619.88 (458.44, 924.25)	659.5 (473.44, 943.59)	0.34
Median CRP [mg/dL]	5.75 (2.43, 10.61)	6.32 (2.22, 9.74)	4.34 (1.56, 9.41)	0.56
Median hs-Tn I [ng/mL]	0.007 (0.005-0.01)	0.006 (0.04-0.11)	0.008 (0.005-0.02)	0.15
Median creatine kinase [IU/mL]	128.4 (70.15, 326)	115.45 (66.3, 194.52)	103.4 (73.75, 198.25)	0.47
Median MB-creatine kinase [IU/mL]	1.1 (0.4, 2.42)	1.19 (0.63, 2.06)	1.25 (0.5, 2.2)	0.79
Chloroquine	2 (3%)	2 (3%)	1 (1%)	0.87
Azithromycin	3 (4%)	3 (4%)	7 (10%)	0.31
Remdesivir	3 (4%)	0 (0%)	1 (1%)	0.13
Convalescent plasma	2 (3%)	2 (3%)	0 (0%)	0.47
Supplemental oxygen	12 (17%)	11 (15%)	10 (14%)	0.88
Fluids	9 (13%)	8 (11%)	10 (14%)	0.88
Heparin	11 (15%)	8 (11%)	9 (12%)	0.72
Acetylsalicylic acid	8 (11%)	11 (15%)	12 (17%)	0.62
Noninvasive mechanical ventilation	0 (0%)	2 (3%)	1 (1%)	0.77
ACE-inhibitors	16 (23%)	15 (21%)	16 (22%)	0.96
Beta-blockers	27 (38%)	28 (39%)	19 (26%)	0.21
Statins	13 (18%)	25 (35%)	20 (28%)	0.08
Antidiabetic medications	14 (20%)	16 (22%)	12 (17%)	0.70
Other antiplatelet agents	6 (3%)	1 (1%)	4 (6%)	0.37
Diuretics	43 (20%)	14 (19%)	14 (19%)	0.95
Sartans	37 (17%)	14 (19%)	7 (10%)	0.10

Data are shown as mean (interquartile range) or mean ± standard deviation (SD) or number (percentage). ACE — angiotensin-converting enzyme; ALT — alanine transaminase; bpm — beats per minute; COPD — chronic obstructive pulmonary disease; CRP — C-reactive protein; hs — high sensitivity; MB — myocardium brain; mcL — microliters; ng/mL — nanograms per milliliter; NEWS2 — National Early Warning Score 2; PO2/FiO2 — arterial partial oxygen pressure in mmHg to fraction of inspired oxygen ratio; Tn — troponin; WBC — white blood cell

Table 2. Outcomes in the intention-to-treat population.

	Amiodarone (n = 71)	Verapamil (n = 72)	Usual care (n = 72)	P
Median time to clinical improvement [days]	9 (6.5, 13)	9 (5, 12)	9 (6, 12.5)	0.65
Clinical category improvement at 15 days	40 (56.3%)	49 (68.1%)	49 (68.1%)	0.41
Clinical category improvement at 28 days	54 (76.4%)	51 (70.45)	50 (69.4%)	0.60
Death	6 (8.5%)	3 (4.2%)	3 (4.2%)	0.43
Median days of oxygen therapy	7 (2, 11)	6 (2, 10.75)	6 (2.25,10.75)	0.90
Median days of hospitalization	14 (10, 15.25)	13 (10.25, 17)	13 (11,15.75)	0.96
Hospitalization in intensive care unit	3 (4%)	4 (6%)	1 (1%)	0.45
Mechanical ventilation	9 (12.6%)	7 (9.72%)	6 (8.33%)	0.68
NEWS2 ≤ 2 at 28 days	56 (78.8%)	61 (84.7%)	61 (84.7%)	0.47

Data are shown as mean (interquartile range) or number (percentage); NEWS2 — National Early Warning Score 2

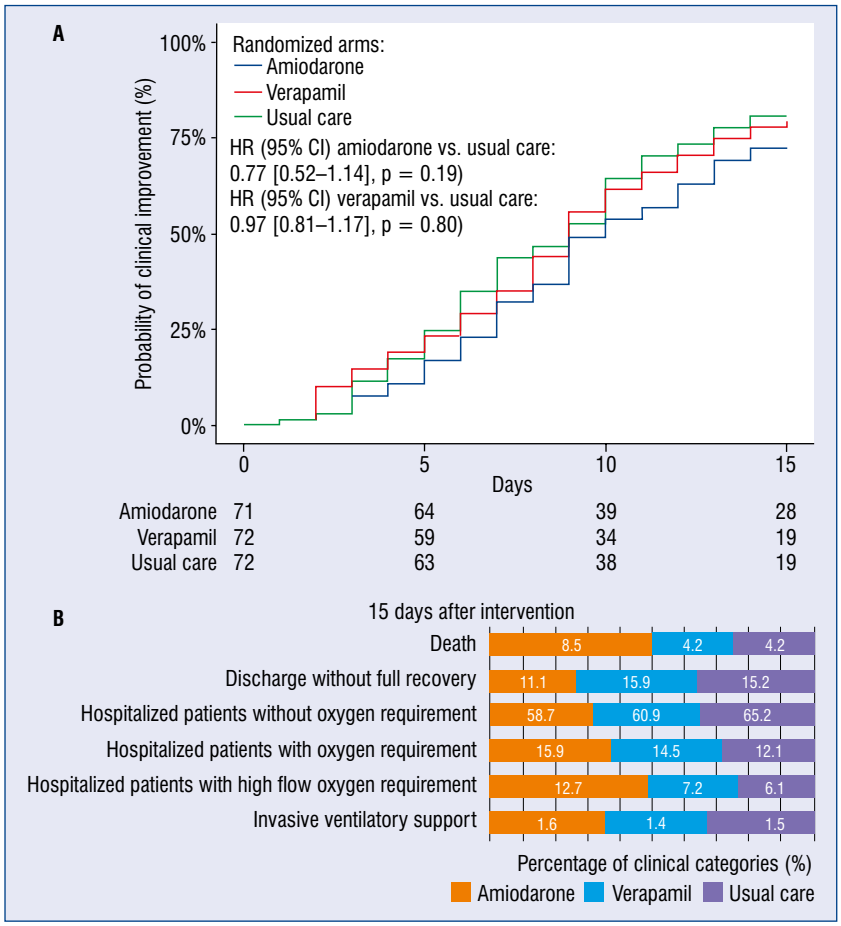

Figure 2. Clinical improvement at 15 days among patients treated with amiodarone or verapamil versus usual care alone; **A.** Kaplan-Meier curves of the time to clinical improvement in the intention-to-treat population; **B.** Distribution of clinical status according to the percentage of clinical categories; CI — confidence interval; HR — hazard ratio.

were 0.77 (0.52–1.14, p = 0.19) with amiodarone and 0.97 (0.81–1.17, p = 0.80) with verapamil as compared to usual care (Fig. 2A); at 28 days, the respective HRs were 0.81 (0.57–1.16, p = 0.26) and 0.81 (0.57–1.16, p = 0.26). At 15 and 28 days, no significant differences were observed among

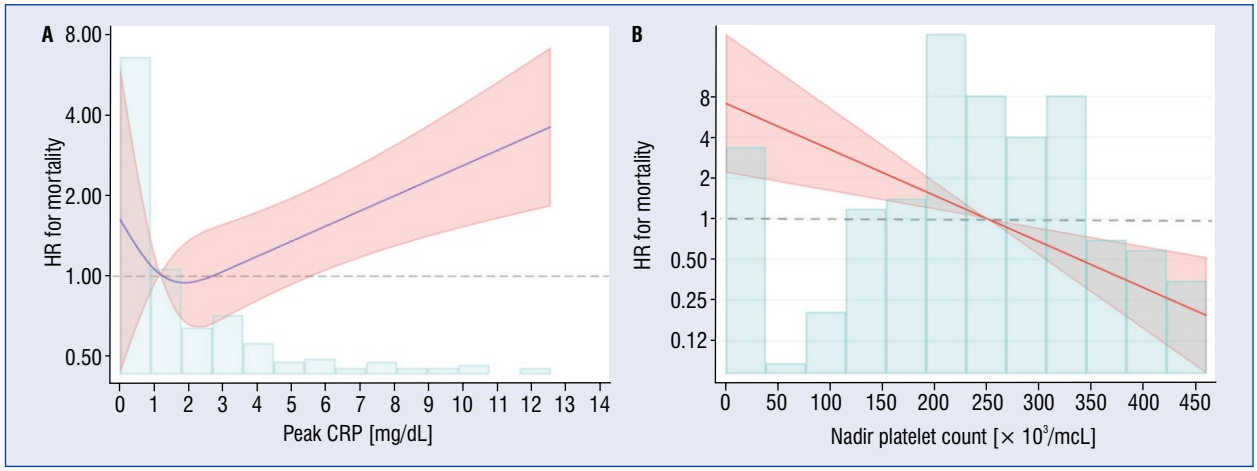

Figure 3. A. Mortality hazard ratios (HRs) according to peak C-reactive protein (CRP). Data were fitted with a restricted cubic spline Cox regression model. The background histograms in light blue represent the percent of density distribution of peak CRP in the study population. Heavy central lines represent HRs with shaded ribbons denoting 95% confidence intervals. The value of 1 (median) served as reference value in presenting the estimated mortality HRs; **B.** Mortality HRs according to nadir platelet count. Data were fitted with a restricted cubic spline Cox regression model. The background histograms in light blue represent the percent of density distribution of nadir platelet count in the study population. Heavy central lines represent HRs with shaded ribbons denoting 95% confidence intervals. The value of 250 (median) served as reference value in presenting the estimated mortality HRs.

groups in clinical outcome ordinal scale categories (Fig. 2B, Table 2). Similarly, hospitalization days were not significantly different among the amiodarone (14 [10–15.3]), verapamil (13 [10.3–17]) and usual care (13 [11–15.8]) arms (Table 2).

Biomarker analyses and phenomapping

CRP, platelet count and mortality. At 28-day follow-up, 12 (5.6%) of 215 patients had died. Based on the estimated restricted cubic spline model, an overall linear association between peak CRP levels and mortality rates was observed (Wald test = 0.78, p for non-linearity = 0.37). In particular, a possible departure from linearity was limited to values below the median peak CRP level of 1 mg/dL, but the confidence intervals were wide (Fig. 3A). Every 5 mg/dL increment in peak CRP was estimated to increase mortality rates by 73% (HR 1.73, 95% CI 1.27–2.37, p = 0.001; Fig. 3A). Data were in agreement with an overall linear association between nadir platelet count and mortality rates (Wald test = 1.43, p for non-linearity = = 0.23), with every 100 × 10^3 per mcL decrement in nadir platelet count increasing the risk of dying by two-fold (HR 2.19, 95% CI 1.37–3.51, p = 0.001; Fig. 3B). By stratified analysis, CRP levels were markedly higher at all time points after randomization in patients who died compared to survivors (Fig. 4A) and in patients without clinical improvement compared to those who improved (**Suppl. Fig. 1**). Nadir platelet counts were lower in subjects who died in comparison to survivors at all time points (Fig. 4B). No statistically significant associations were found between other explored biomarkers and mortality, with the exception of median peak D-dimer: 753 (500–946) ng/mL in nonsurvivors versus 665 (443–700) ng/ml in survivors (p = 0.03) (**Suppl. Table 1**).

Phenomapping. An artificial intelligence-driven variable selection algorithm was applied to a total of 46 clinical and biomarker variables (**Suppl. Table 2**) with retainment of peak CRP and nadir platelet count as the most informative features. On the basis of minimal intra- and within-cluster variation, an optimal number of 4 clusters was selected. The population was then divided into 4 phenotypes, the 4th of which had the greatest peak CRP values (median 5 mg/dL) and lowest nadir platelet counts (median 187 × 10^3/mcL), that in turn was associated with significantly higher 28-day mortality in comparison to the other 3 clusters (p = 0.02, Fig. 5A, B). A cluster plot with 4 phenotypes was generated (**Suppl. Fig. 2**).

Safety

At day 15 no significant increase of serious adverse events was observed in the amiodarone or verapamil arms compared to the control group,

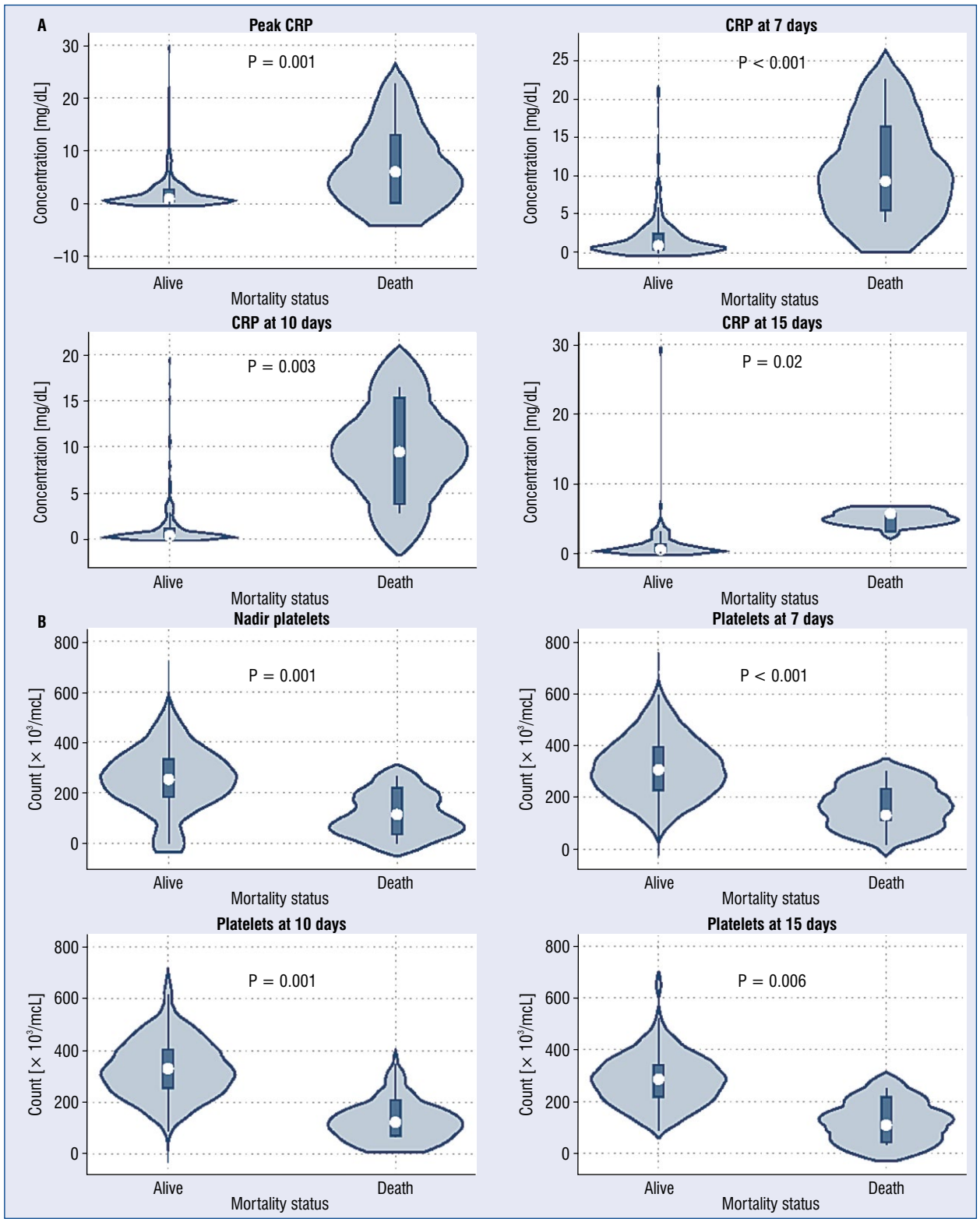

Figure 4. A. Violin plots of peak C-reactive protein (CRP) values and CRP levels at 7, 10 and 15 days after randomization in patients who survived or died during the study. The width of each region corresponds to the frequency of data points in each part of the violin. Densities are accompanied by an overlaid box plot to provide additional information. The circle denotes the median and the box limits the 25th and 75th percentiles; **B.** Violin plots of nadir platelet count values and platelet counts at 7, 10 and 15 days after randomization in patients who survived or died during the study. The width of each region corresponds to the frequency of data points in each part of the violin. Densities are accompanied by an overlaid box plot to provide additional information. The circle denotes the median and the box limits the 25th and 75th percentiles.

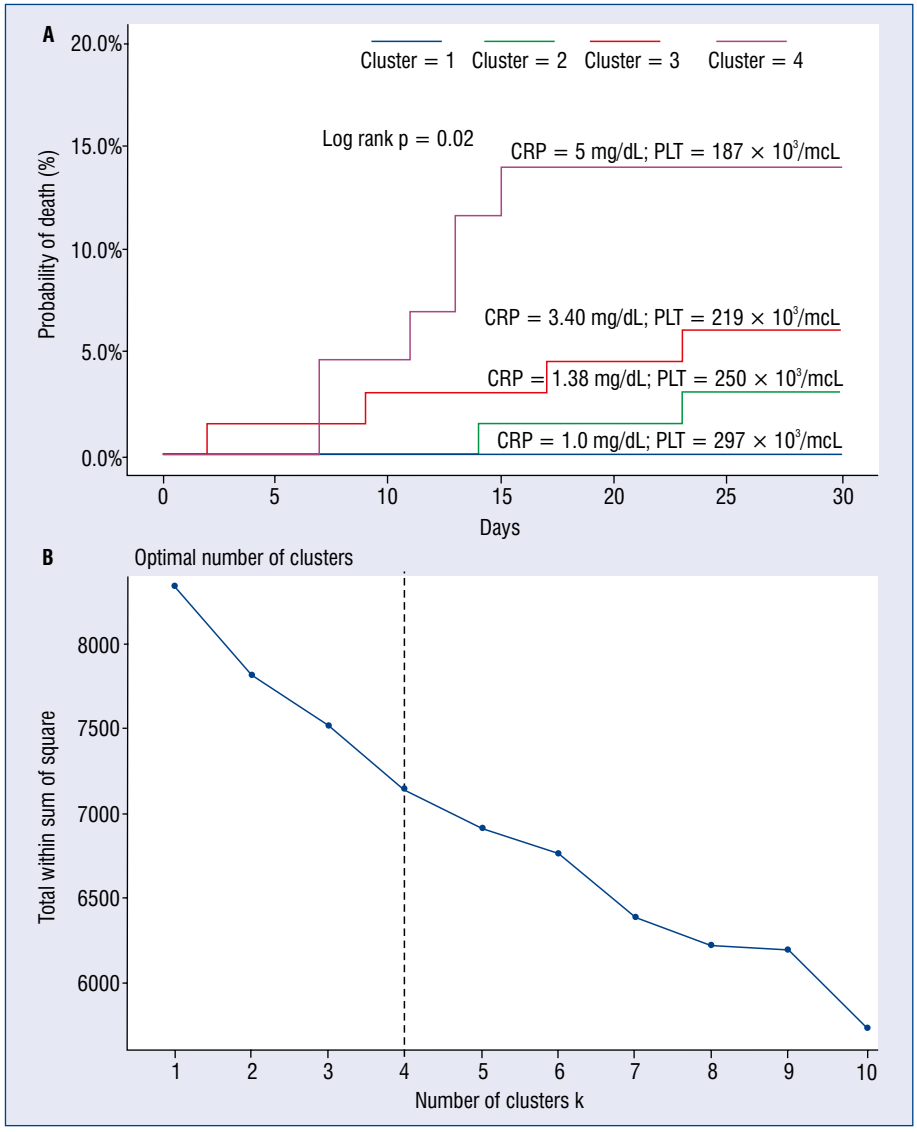

Figure 5. A. Kaplan-Meier mortality curves of patients belonging to 4 distinct biomarker phenotypes generated by cluster analysis. Patient median values of peak C-reactive protein (CRP) and nadir platelet count are shown stratified by phenogroup; **B.** Algorithm plot of the optimal number of clusters using the sum of squares method. The location of a bend (knee) in the plot is generally considered an indicator of the appropriate number of clusters; PLT — platelet count.

including second- or third-degree atrioventricular blocks, other bradyarrhythmias or ventricular tachyarrhythmias (**Suppl. Table 3**). No significant prolongation of the QT or corrected QT intervals was recorded in patients treated with amiodarone and verapamil versus usual care alone (**Suppl. Table 3**).

Discussion

This multicenter randomized trial enrolling symptomatic hospitalized nonintensive-care patients with COVID-19 did not detect any significant differences in the rates of clinical improvement among patients randomized to amiodarone or verapamil on top of usual supportive care as compared to patients randomized to usual care alone. However, the trial was underpowered, given the slow enrollment and recruitment of 215 out of 804 planned patients (26.7%). Thus, although no apparent trend was noted by adding an ion channel inhibitor on top of usual care, the findings should be considered preliminary.

In contrast, the prespecified individual and cluster laboratory-based analyses showed: 1) Significantly increased mortality across levels of peak CRP and nadir platelet counts; 2) An inverse association between CRP and clinical

improvement; 3) Cluster-analysis identification of distinct phenotypes with highest mortality in the cluster with higher CRP and lowest platelet count (median 5 mg/dL CRP and median 187 × 10^3/mcL, respectively); 4) Patterns of increased mortality for increasing CRP and decreasing platelet count modeled on serial measurements at 7, 10 and 15 days after randomization.

Ion channels have been recently suggested as a potential important target for present and future major viral infections owing to the emerging role of ions in viral membrane entry and fusion [14, 15]. RECOVERY-SIRIO is the first dedicated randomized trial to have addressed the effect of ion-channel inhibition in COVID-19. It was found that amiodarone and verapamil, two cardiovascular agents with ion-channel inhibitor actions, did not improve the clinical status of hospitalized nonintensive-care COVID-19 patients. The prespecified serial laboratory assessments in the present trial offered the opportunity to conduct an in-depth investigation of a set of candidate predictive parameters in relation to clinical outcomes. In the current study, both peak CRP and nadir platelet count were most significantly related to increased mortality and peak CRP alone to lack of clinical improvement in hospitalized initially nonintensive-care patients with COVID-19. The notion that systemic inflammatory response to severe SARS-CoV-2 infection contributes to disease severity has been confirmed in several reports [16]. During the advanced stages of COVID-19 a cytokine storm response can be triggered which is, in turn, associated with high mortality. The released cytokines stimulate hepatocytes to produce CRP [17].

Prior retrospective reports showed increased CRP trends in COVID-19 patients who eventually died compared to survivors [18, 19]. Similar CRP, although less robust, is a significant association between mortality and nadir platelet count found in the present study. Thrombocytopenia has been detected in 58–95% of severe cases of COVID-19 [20]. Additionally, nonsurvivors have been reported to have lower platelet count than survivors [21]. The current study extends these earlier results in the context of a randomized trial conducted with balanced patient characteristics and prospective serial laboratory assessments at predefined time points. The extent to which CRP could serve as a quantitative reliable prognostic marker during the relatively early phases of COVID-19 among symptomatic hospitalized nonintensive-care patients, particularly when combined with platelet count, remains incompletely known.

According to available research, this is the first study to prospectively address by a quantitative serial approach to the combined predictive role of inflammation and platelets during the early stages of nonintensive-care COVID-19 patients and to have applied an artificial intelligence algorithm to the randomized trial population that contributed to unveil meaningful phenotypes within COVID-19 based on distinct values of peak CRP and nadir platelet count. The laboratory-focused analytical approach applied in the current trial provided a more nuanced appraisal between CRP level and mortality risk in COVID-19. The analyses conducted allowed for the identification of a significant gradient for mortality across levels of peak CRP and nadir platelet counts.

More specifically, a relation was found between CRP and mortality with progressive risk increments when peak CRP was above the 1 mg/dL threshold. When CRP values exceeded 4–5 mg/dL the risk of mortality became approximately three-fold greater in comparison to patients with CRP values below 1 mg/dL. Recent advances in artificial intelligence, namely machine learning-based clustering methodologies, explicitly model the inherent nature of data directly. Accordingly, unsupervised clustering was applied to the laboratory data of this study that ultimately provided a phenotypic stratification. The two most important variables retained were peak CRP and nadir platelet count. These two factors allowed the identification of four distinct phenotypic subgroups, of which the 4^{th} (median 5 mg/dL peak CRP and median 187 × 10^3/mcL nadir platelet count) was associated with the greatest mortality risk.

In contrast, no significant associations were found between other explored biomarkers and mortality, with the exception of peak D-dimer that was however of lower magnitude than peak CRP and nadir platelet count. These findings trigger arguments for prioritization of the assessment of the latter two biomarkers to attain optimal early risk stratification in COVID-19. In addition to their significant association with mortality and disease progression, one practical advantage to track CRP and platelet count is that they are routine laboratory tests.

Clinical improvement, based on a clinical severity scale, has been widely implemented as a standardized clinical endpoint in COVID-19 trials. However, the appropriate summary measure for severity scores has been a matter of debate, particularly given the variable time course of COVID-19, the heterogeneous clinical presentation of the disease [22] and the subjectiveness of clinical

interventions and categorization [23]. In the current study, tracking practical laboratory parameters allowed precise early stratification of the risk of dying and prediction of disease progression in COVID-19. Sensitive biomarkers measured as continuous variables, such as peak CRP and nadir platelet count, may offer a reliable outcome prediction and avoid the loss of statistical power that occurs instead when categorical variables such as clinical improvement ordinal scales or a binary 'recovered' versus 'not recovered' status is used. Further dedicated randomized studies are warranted to test the hypothesis of biomarker-based endpoints.

Limitations of the study

The trial was stopped prematurely because of significant abatement of COVID-19 cases in the country in 2021 and slow-enrollment. Therefore, it was not possible to exclude that differences in improvement rates could have emerged had the trial been larger. The study was conducted with an open-label design; however, the lack of a blind placebo control arm is mitigated by the adjudication of events performed by an independent event committee not involved in the study.

Conclusions

In this randomized trial ion channel inhibition with amiodarone or verapamil was not found to significantly accelerate short term clinical improvement in symptomatic hospitalized nonintensive-care COVID-19 patients, although the study was underpowered for this endpoint owing to premature trial conclusion. In contrast, the trial allowed to quantitatively and serially assess the prognostic role of the combination of peak C-reactive protein and nadir platelet count which were significantly associated with mortality and disease progression. Whether early risk stratification with these practical laboratory tests can modify prognosis and guide therapies can be tested in dedicated studies.

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Conflict of interest: None declared

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Diagnostic value of lactate dehydrogenase in COVID-19: A systematic review and meta-analysis

Bartosz Fialek[1], Michal Pruc[2], Jacek Smereka[2, 3], Rafal Jas[4], Mansur Rahnama-Hezavah[5], Andrea Denegri[6], Agnieszka Szarpak[7], Milosz J. Jaguszewski[8], Frank W. Peacock[9], Lukasz Szarpak[9]

[1]Rheumatology Department, Marshal Jozef Pilsudski Memorial Hospital, Plonsk, Poland
[2]Research Unit, Polish Society of Disaster Medicine, Warsaw, Poland
[3]Department of Emergency Medical Service, Wroclaw Medical University, Wroclaw, Poland
[4]Students Research Club, Maria Sklodowska-Curie Medical Academy, Warsaw, Poland
[5]Chair and Department of Oral Surgery, Medical University of Lublin, Poland
[6]Parma University Hospital, Parma, Italy
[7]Institute of Outcomes Research, Maria Sklodowska-Curie Medical Academy, Warsaw, Poland
[8]1st Department of Cardiology, Medical University of Gdansk, Poland
[9]Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine Houston, Houston, TX, United States

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Abstract

Background: *This meta-analysis outlines the role of elevated lactate dehydrogenase (LDH) levels in assessing the severity of coronavirus disease 2019 (COVID-19).*

Methods: *The current study was designed as a systematic review and meta-analysis. Embase, PubMed, Web of Science, Scopus and Cochrane Central Register of Controlled Trials were searched to identify the usefulness of LDH as a marker of COVID-19 severity. All extracted data were analyzed using RevMan V.5.4 or STATA V.14 software.*

Results: *A total of 264 records were selected for this meta-analysis. Pooled analysis showed that LDH levels were statistically significantly lower in the group of survivors compared to patients who died in hospital (standardized mean differences [SMD] = –3.10; 95% confidence interval [CI]: –3.40 to –2.79; I^2 = 99%; p < 0.001). Lower LDH levels were observed in non-severe groups compared to severe course of COVID-19 (SMD = –2.38; 95% CI: –2.61 to –2.14; I^2 = 99%; p < 0.001). The level of LDH was statistically significantly lower in the severe group compared to the critical group (SMD = –1.48; 95% CI: –2.04 to –0.92; I^2 = 98%; p < 0.001). Patients who did not require treatment in the intensive care unit (ICU) showed significantly lower levels of LDH compared to patients who required treatment in the ICU (SMD = –3.78; 95% CI: –4.48 to –3.08; I^2 = 100%; p < 0.001).*

Conclusions: *This meta-analysis showed that elevated LDH was associated with a poor outcome in COVID-19.* (Cardiol J 2022; 29, 5: 751–758)

Key words: lactate dehydrogenase, LDH, marker, severity, COVID-19, SARS-CoV-2, meta-analysis

Address for correspondence: Lukasz Szarpak, Assoc. Prof., PhD, DPH, DBA, LL.M., Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine, Ben Taub Hospital, 1504 Taub Loop, Houston, TX 77030, United States, e-mail: lukasz.szarpak@bcm.edu

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has become a public health threat worldwide and have caused significant economic problems in many countries [1, 2]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pathogen and the disease caused by this virus, COVID-19, are not yet fully understood. In patients infected with SARS-CoV-2, there is a wide variation in the symptoms and forms of the disease, which depends on both patient-related factors, infection, and the virus itself. The main symptoms of infection with the new coronavirus include headache, elevated body temperature/fever, fatigue, cough, dyspnea, myalgia, and arthralgia [3, 4]. A severe course of the disease is observed in some cases, with a high risk of death associated with respiratory failure, circulatory failure, and multiple organ failure [5, 6].

After active infection with SARS-CoV-2 has resolved, up to 10% to as many as 30% of recovered patients may suffer from complaints in a symptom complex called long COVID-19. SARS-2 coronavirus infection also shows the potential to induce a generalized inflammatory response, which is directly related to the severity of the course of COVID-19 [7–9]. In addition to interleukin (IL)-6, whose role in inducing generalized inflammation is the most significant [10], increased levels of other inflammatory exponents were also observed, such as Il-2, Il-7, Il-10, TNF, G-CSF, MCP1, MIP1, CXCL10, C-reactive protein, ferritin, D-dimer [11–20].

It is critical to rapidly identify factors contributing to the severity of the disease and indicators of a potentially severe course of COVID-19. In the clinical context, it has become essential to find markers that could predict the severity of the course of COVID-19. Determination of such a marker would allow early assessment of the course of COVID-19 and qualification of the patient for appropriate primarily therapeutic management [21]. It would also positively impact the monitoring of the COVID-19 patient's condition and extend medical supervision to patients who meet the criteria for severe COVID-19.

One potential biomarker whose elevated blood levels could herald the severity of COVID-19 is lactate dehydrogenase (LDH) — an intracellular enzyme that plays a role in energy production [22, 23]. An increased concentration of this enzyme in the blood was observed in tissue damage and subsequent cell death, hypoxia (in the course of respiratory failure), diseases of the hematopoietic and lymphatic systems, or inflammation of the lungs, pericardium, and pancreas. The highest concentrations are found in the heart, lungs, liver, and skeletal muscle. In many cases of severe COVID-19, an increase in LDH activity was observed, which may be due to cell damage as well as impaired blood flow and oxygen delivery.

This meta-analysis outlines the role of elevated LDH levels in assessing the severity of COVID-19. This analysis was based on recent studies, including those involving new virus variants, and included an extensive group of patients and a wide range of publications.

Methods

The present study was designed as a systematic review and meta-analysis, performed in accordance to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [24].

Data source and retrieval strategy

Two reviewers (B.F. and M.P.) comprehensively searched electronic databases (Embase, PubMed, Web of Science, Scopus and Cochrane Central Register of Controlled Trials) from their inception to April 2022. The following search terms were used: "lactate dehydrogenase" OR "LDH" AND "COVID-19" OR "SARS-CoV-2" OR "novel coronavirus".

Studies published in English, involving adult patients with COVID-19 were included in the study. Studies on the pediatric population, illustrative studies, meta-analyzes, editorials, also an inability to collect complete data or to get the full text were excluded.

Data extraction and literature quality evaluation

Two researchers (B.F. and M.P.) independently conducted literature screening and extraction to the inclusion and exclusion criteria. If there were different opinions, the matter was discussed and resolved through discussion with a third researcher (L.S.). Data were collected using a predesigned form. For each study, the following information was extracted: publication (last name of the first author, year of publication), LDH levels in predefined groups (survivor vs. non-survivor; non-severe vs. severe group; severe vs. critical group; non-intensive care unit [ICU] vs. ICU admission group).

The quality of each article was evaluated by the same researchers as above, using a previously piloted standardized form and the Newcastle-Ottawa scale [25].

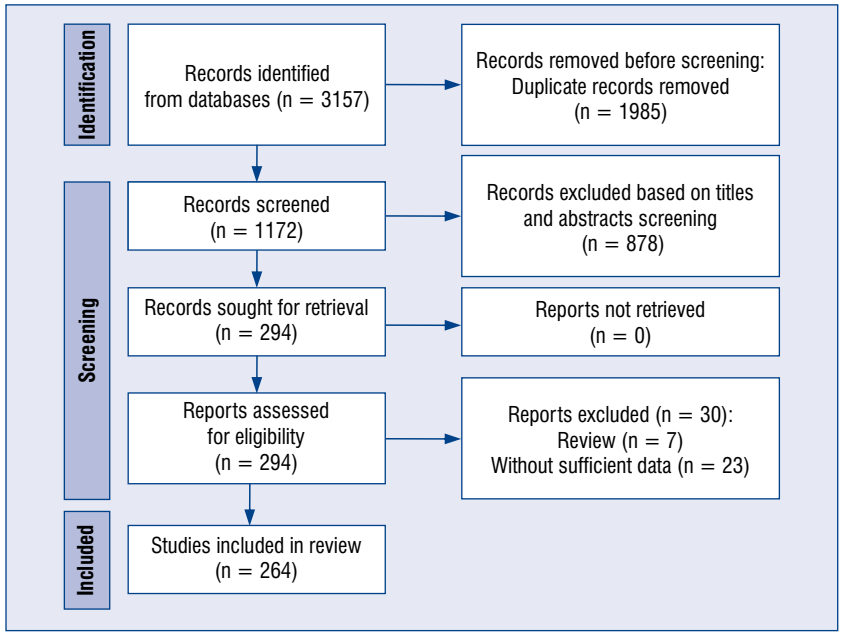

Figure 1. Database search and selection of studies according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

Statistical analysis

The STATA 14 software (StataCorp LP, College Station, USA) and RevMan 5.4 software (Cochrane Collaboration, UK) were used for data analysis in this meta-analysis. For dichotomous data, odds ratios (ORs) were used as the effect measure with 95% confidence intervals (CIs), and for continuous data, standardized mean differences (SMDs) with 95% CI were applied. When LDH values were reported as median and interquartile range, the estimated means and standard deviations using the formula described by Hozo et al. [26] were also utilized. Heterogeneity was assessed with the I^2 statistic, in which the results ranged from 0% to 100%. Heterogeneity was interpreted as not observed when $I^2 = 0\%$, low when $I^2 = 25\%$, medium when $I^2 = 50\%$, and high when $I^2 = 75\%$ [27]. For the meta-analysis, the random-effects model was used (assuming a distribution of effects across studies) to weight estimates of studies in proportion to their significance [28]. $P < 0.05$ was considered statistically significant.

Results

Literature search results

The systematic search identified 3157 potential articles. As is shown in Figure 1, 294 reports met the inclusion criteria, and 30 were excluded for insufficient data after full text screening. A total of 264 records were selected for this meta-analysis. The Newcastle Ottawa Scale scores of the 264 included studies were ≥ 7.

Meta-analysis results

One hundred and thirty studies reported LDH levels among survivor and non-survivor groups. Pooled analysis showed that LDH levels were statistically significantly lower in the group of survivors compared to patients who died in hospital (SMD = –3.10; 95% CI: –3.40 to –2.79; $I^2 = 99\%$; $p < 0.001$; Fig. 2).

One hundred and two studies showed LDH levels in non-severe vs. severe COVID-19 patient group. Pooled analysis showed lower LDH levels in non-severe groups compared to severe course of COVID-19 (SMD = –2.38; 95% CI: –2.61 to –2.14; $I^2 = 99\%$; $p < 0.001$; Fig. 3).

Lactate dehydrogenase levels in the severe group compared with patients who had a critical course of COVID-19 were reported in 15 articles. The level of LDH was statistically significantly lower in the severe group compared to the critical group (SMD = –1.48; 95% CI: –2.04 to –0.92; $I^2 = 98\%$; $p < 0.001$; Fig. 4).

Patients who did not require treatment in the ICU showed significantly lower levels of LDH compared to patients who required treatment in the ICU (SMD = –3.78; 95% CI: –4.48 to –3.08; $I^2 = 100\%$; $p < 0.001$; Fig. 5).

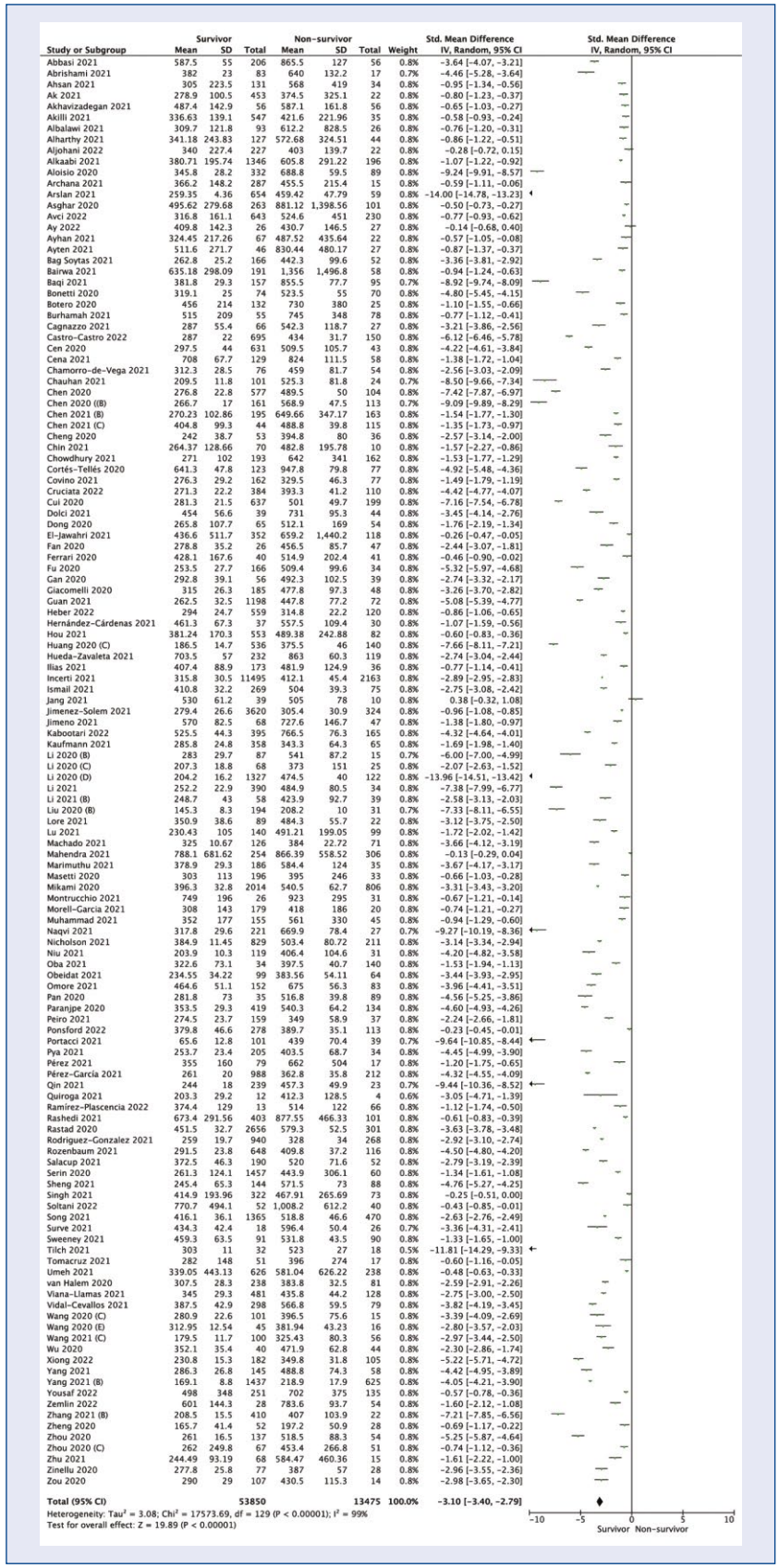
Survivor
Non-survivor
Std. Mean Difference
Std. Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Abbasi 2021 587.5 55 206 865.5 127 56 0.8% −3.64 [−4.07, −3.21]
Abrishami 2021 382 23 83 640 132.2 17 0.7% −4.46 [−5.28, −3.64]
Ahsan 2021 305 223.5 131 568 419 34 0.8% −0.95 [−1.34, −0.56]
Ak 2021 278.9 100.5 453 374.5 325.1 22 0.8% −0.80 [−1.23, −0.37]
Akhavizadegan 2021 487.4 142.9 56 587.1 161.8 56 0.8% −0.65 [−1.03, −0.27]
Akilli 2021 336.63 139.1 547 421.6 221.96 35 0.8% −0.58 [−0.93, −0.24]
Albalawi 2021 309.7 121.8 93 612.2 828.5 26 0.8% −0.76 [−1.20, −0.31]
Alharthy 2021 341.18 243.83 127 572.68 324.51 44 0.8% −0.86 [−1.22, −0.51]
Aljohani 2022 340 227.4 227 403 139.7 22 0.8% −0.28 [−0.72, 0.15]
Alkaabi 2021 380.71 195.74 1346 605.8 291.22 196 0.8% −1.07 [−1.22, −0.92]
Aloisio 2020 345.8 28.2 332 688.8 59.5 89 0.8% −9.24 [−9.91, −8.57]
Archana 2021 366.2 148.2 287 455.5 215.4 15 0.8% −0.59 [−1.11, −0.06]
Arslan 2021 259.35 4.36 654 459.42 47.79 59 0.8% −14.00 [−14.78, −13.23]
Asghar 2020 495.62 279.68 263 881.12 1,398.56 101 0.8% −0.50 [−0.73, −0.27]
Avci 2022 316.8 161.1 643 524.6 451 230 0.8% −0.77 [−0.93, −0.62]
Ay 2022 409.8 142.3 26 430.7 146.5 27 0.8% −0.14 [−0.68, 0.40]
Ayhan 2021 324.45 217.26 67 487.52 435.64 22 0.8% −0.57 [−1.05, −0.08]
Ayten 2021 511.6 271.7 46 830.44 480.17 27 0.8% −0.87 [−1.37, −0.37]
Bag Soytas 2021 262.8 25.2 166 442.3 99.6 52 0.8% −3.36 [−3.81, −2.92]
Bairwa 2021 635.18 298.09 191 1,356 1,496.8 58 0.8% −0.94 [−1.24, −0.63]
Baqi 2021 381.8 29.3 157 855.5 77.7 95 0.7% −8.92 [−9.74, −8.09]
Bonetti 2020 319.1 25 74 523.5 55 70 0.8% −4.80 [−5.45, −4.15]
Botero 2020 456 214 132 730 380 25 0.8% −1.10 [−1.55, −0.66]
Burhamah 2021 515 209 55 745 348 78 0.8% −0.77 [−1.12, −0.41]
Cagnazzo 2021 287 55.4 66 542.3 118.7 27 0.8% −3.21 [−3.86, −2.56]
Castro-Castro 2022 287 22 695 434 31.7 150 0.8% −6.12 [−6.46, −5.78]
Cen 2020 297.5 44 631 509.5 105.7 43 0.8% −4.22 [−4.61, −3.84]
Cena 2021 708 67.7 159 824 111.5 58 0.8% −1.38 [−1.72, −1.04]
Chamorro-de-Vega 2021 312.3 28.5 76 459 81.7 54 0.8% −2.56 [−3.03, −2.09]
Chauhan 2021 209.5 11.8 101 525.3 81.8 24 0.7% −8.50 [−9.66, −7.34]
Chen 2020 276.8 22.8 577 489.5 50 104 0.8% −7.42 [−7.87, −6.97]
Chen 2020 ((B) 266.7 17 161 568.9 47.5 113 0.7% −9.09 [−9.89, −8.29]
Chen 2021 (B) 270.23 102.86 195 649.66 347.17 163 0.8% −1.54 [−1.77, −1.30]
Chen 2021 (C) 404.8 99.3 44 488.8 39.8 115 0.8% −1.35 [−1.73, −0.97]
Cheng 2020 242 38.7 53 394.8 80 36 0.8% −2.57 [−3.14, −2.00]
Chin 2021 264.37 128.66 70 482.8 195.78 10 0.8% −1.57 [−2.27, −0.86]
Chowdhury 2021 271 102 193 642 341 162 0.8% −1.53 [−1.77, −1.29]
Cortés-Tellés 2020 641.3 47.8 123 947.8 79.8 77 0.8% −4.92 [−5.48, −4.36]
Covino 2021 276.3 29.2 162 329.5 46.3 77 0.8% −1.49 [−1.79, −1.19]
Cruciata 2022 271.3 22.2 384 393.3 41.2 110 0.8% −4.42 [−4.77, −4.07]
Cui 2020 281.3 21.5 637 501 49.7 199 0.8% −7.16 [−7.54, −6.78]
Dolci 2021 454 56.6 39 731 95.3 44 0.8% −3.45 [−4.14, −2.76]
Dong 2020 265.8 107.7 65 512.1 169 54 0.8% −1.76 [−2.19, −1.34]
El-Jawahri 2021 436.6 511.7 352 659.2 1,440.2 118 0.8% −0.26 [−0.47, −0.05]
Fan 2020 278.8 35.2 26 456.5 85.7 47 0.8% −2.44 [−3.07, −1.81]
Ferrari 2020 428.1 167.6 40 514.9 202.4 41 0.8% −0.46 [−0.90, −0.02]
Fu 2020 253.5 27.7 166 509.4 99.6 34 0.8% −5.32 [−5.97, −4.68]
Gan 2020 292.8 39.1 56 492.3 102.5 39 0.8% −2.74 [−3.32, −2.17]
Giacomelli 2020 315 26.3 185 477.8 97.3 48 0.8% −3.26 [−3.70, −2.82]
Guan 2021 262.5 32.5 1198 447.8 77.2 72 0.8% −5.08 [−5.39, −4.77]
Heber 2022 294 24.7 559 314.8 22.2 120 0.8% −0.86 [−1.06, −0.65]
Hernández-Cárdenas 2021 461.3 67.3 37 557.5 109.4 30 0.8% −1.07 [−1.59, −0.56]
Hou 2021 381.24 170.3 553 489.38 242.88 82 0.8% −0.60 [−0.83, −0.36]
Huang 2020 (C) 186.5 14.7 536 375.5 46 140 0.8% −7.66 [−8.11, −7.21]
Hueda-Zavaleta 2021 703.5 57 232 863 60.3 119 0.8% −2.74 [−3.04, −2.44]
Ilias 2021 407.4 88.9 173 481.9 124.9 36 0.8% −0.77 [−1.14, −0.41]
Incerti 2021 315.8 30.5 11495 412.1 45.4 2163 0.8% −2.89 [−2.95, −2.83]
Ismail 2021 410.8 32.2 269 504 39.3 75 0.8% −2.75 [−3.08, −2.42]
Jang 2021 530 61.2 39 505 78 10 0.8% 0.38 [−0.32, 1.08]
Jimenez-Solem 2021 279.4 26.6 3620 305.4 30.9 324 0.8% −0.96 [−1.08, −0.85]
Jimeno 2021 570 82.5 68 727.6 146.7 47 0.8% −1.38 [−1.80, −0.97]
Kabootari 2022 525.5 44.3 395 766.5 76.3 165 0.8% −4.32 [−4.64, −4.01]
Kaufmann 2021 285.8 24.8 358 343.3 64.3 65 0.8% −1.69 [−1.98, −1.40]
Li 2020 (B) 283 29.7 87 541 87.2 15 0.7% −6.00 [−7.00, −4.99]
Li 2020 (C) 207.3 18.8 68 373 151 25 0.8% −2.07 [−2.63, −1.52]
Li 2020 (D) 204.2 16.2 1327 474.5 40 122 0.8% −13.96 [−14.51, −13.42]
Li 2021 252.2 22.9 390 484.9 80.5 34 0.8% −7.38 [−7.99, −6.77]
Li 2021 (B) 248.7 43 58 423.9 92.7 39 0.8% −2.58 [−3.13, −2.03]
Liu 2020 (B) 145.3 8.3 194 208.2 10 31 0.7% −7.33 [−8.11, −6.55]
Lore 2021 350.9 38.6 89 484.3 55.7 22 0.8% −3.12 [−3.75, −2.50]
Lu 2021 230.43 105 140 491.21 199.05 99 0.8% −1.72 [−2.02, −1.42]
Machado 2021 325 10.67 126 384 22.72 71 0.8% −3.66 [−4.12, −3.19]
Mahendra 2021 788.1 681.62 254 866.39 558.52 306 0.8% −0.13 [−0.29, 0.04]
Marimuthu 2021 378.9 29.3 186 584.4 124 35 0.8% −3.67 [−4.17, −3.17]
Masetti 2020 303 113 196 395 246 33 0.8% −0.66 [−1.03, −0.28]
Mikami 2020 396.3 32.8 2014 540.5 62.7 806 0.8% −3.31 [−3.43, −3.20]
Montrucchio 2021 749 196 26 923 295 31 0.8% −0.67 [−1.21, −0.14]
Morell-Garcia 2021 308 143 179 418 186 20 0.8% −0.74 [−1.21, −0.27]
Muhammad 2021 352 177 155 561 330 45 0.8% −0.94 [−1.29, −0.60]
Naqvi 2021 317.8 29.6 221 669.9 78.4 27 0.7% −9.27 [−10.19, −8.36]
Nicholson 2021 384.9 11.45 829 503.4 80.72 211 0.8% −3.14 [−3.34, −2.94]
Niu 2021 203.9 10.3 119 406.4 104.6 31 0.8% −4.20 [−4.82, −3.58]
Oba 2021 322.6 73.1 34 397.5 40.7 140 0.8% −1.53 [−1.94, −1.13]
Obeidat 2021 234.55 34.22 99 383.56 54.11 64 0.8% −3.44 [−3.93, −2.95]
Omore 2021 464.6 51.1 152 675 56.3 83 0.8% −3.96 [−4.41, −3.51]
Pan 2020 281.8 73 35 516.8 39.8 89 0.8% −4.56 [−5.25, −3.86]
Paranjpe 2020 353.5 29.3 419 540.3 64.2 134 0.8% −4.60 [−4.93, −4.26]
Peiro 2021 274.5 23.7 159 349 58.9 37 0.8% −2.24 [−2.66, −1.81]
Ponsford 2022 379.8 46.6 278 389.7 35.1 113 0.8% −0.23 [−0.45, −0.01]
Portacci 2021 65.6 12.8 101 439 70.4 39 0.7% −9.64 [−10.85, −8.44]
Pya 2021 253.7 23.4 205 403.5 68.7 34 0.8% −4.45 [−4.99, −3.90]
Pérez 2021 355 160 79 662 504 17 0.8% −1.20 [−1.75, −0.65]
Pérez-García 2021 261 20 988 362.8 35.8 212 0.8% −4.32 [−4.55, −4.09]
Qin 2021 244 18 239 457.3 49.9 23 0.7% −9.44 [−10.36, −8.52]
Quiroga 2021 203.3 29.2 12 412.3 128.5 4 0.6% −3.05 [−4.71, −1.39]
Ramírez-Plascencia 2022 374.4 129 13 514 122 66 0.8% −1.12 [−1.74, −0.50]
Rashedi 2021 673.4 291.56 403 877.55 466.33 101 0.8% −0.61 [−0.83, −0.39]
Rastad 2020 451.5 32.7 2656 579.3 52.5 301 0.8% −3.63 [−3.78, −3.48]
Rodriguez-Gonzalez 2021 259 19.7 940 328 34 268 0.8% −2.92 [−3.10, −2.74]
Rozenbaum 2021 291.5 23.8 648 409.8 37.2 116 0.8% −4.50 [−4.80, −4.20]
Salacup 2021 372.5 46.3 190 520 71.6 52 0.8% −2.79 [−3.19, −2.39]
Serin 2020 261.3 124.1 1457 443.9 306.1 60 0.8% −1.34 [−1.61, −1.08]
Sheng 2021 245.4 65.3 144 571.5 73 88 0.8% −4.76 [−5.27, −4.25]
Singh 2021 414.9 193.96 322 467.91 265.69 73 0.8% −0.25 [−0.51, 0.00]
Soltani 2022 770.7 494.1 52 1,008.2 612.2 40 0.8% −0.43 [−0.85, −0.01]
Song 2021 416.1 36.1 1365 518.8 46.6 470 0.8% −2.63 [−2.76, −2.49]
Surve 2021 434.3 42.4 18 596.4 50.4 26 0.7% −3.36 [−4.31, −2.41]
Sweeney 2021 459.3 63.5 91 531.8 43.5 90 0.8% −1.33 [−1.65, −1.00]
Tilch 2021 303 11 32 523 27 18 0.5% −11.81 [−14.29, −9.33]
Tomacruz 2021 282 148 51 396 274 17 0.8% −0.60 [−1.16, −0.05]
Umeh 2021 339.05 443.13 626 581.04 626.22 238 0.8% −0.48 [−0.63, −0.33]
van Halem 2020 307.5 28.3 238 383.8 32.5 81 0.8% −2.59 [−2.91, −2.26]
Viana-Llamas 2021 345 29.3 481 435.8 44.2 128 0.8% −2.75 [−3.00, −2.50]
Vidal-Cevallos 2021 387.5 42.9 298 566.8 59.5 79 0.8% −3.82 [−4.19, −3.45]
Wang 2020 (C) 280.9 22.6 101 396.5 75.6 15 0.8% −3.39 [−4.09, −2.69]
Wang 2020 (E) 312.95 12.54 45 381.94 43.23 16 0.8% −2.80 [−3.57, −2.03]
Wang 2021 (C) 179.5 11.7 100 325.43 80.3 56 0.8% −2.97 [−3.44, −2.50]
Wu 2020 352.1 35.4 40 471.9 62.8 44 0.8% −2.30 [−2.86, −1.74]
Xiong 2022 230.8 15.3 182 349.8 31.8 105 0.8% −5.22 [−5.71, −4.72]
Yang 2021 286.3 26.8 145 488.8 74.3 58 0.8% −4.42 [−4.95, −3.89]
Yang 2021 (B) 169.1 8.8 1437 218.9 17.9 625 0.8% −4.05 [−4.21, −3.90]
Yousaf 2022 498 348 251 702 375 135 0.8% −0.57 [−0.78, −0.36]
Zemlin 2022 601 144.3 28 783.6 93.7 54 0.8% −1.60 [−2.12, −1.08]
Zhang 2021 (B) 208.5 15.5 410 407 103.9 22 0.8% −7.21 [−7.85, −6.56]
Zheng 2020 165.7 41.4 52 197.2 50.9 28 0.8% −0.69 [−1.17, −0.22]
Zhou 2020 261 16.5 137 518.5 88.3 54 0.8% −5.25 [−5.87, −4.64]
Zhou 2020 (C) 262 249.8 67 453.4 266.8 51 0.8% −0.74 [−1.12, −0.36]
Zhu 2021 244.49 93.19 68 584.47 460.36 15 0.8% −1.61 [−2.22, −1.00]
Zinellu 2020 277.8 25.8 77 387 57 28 0.8% −2.96 [−3.55, −2.36]
Zou 2020 290 29 107 430.5 115.3 14 0.8% −2.98 [−3.65, −2.30]
Total (95% CI) 53850 13475 100.0% −3.10 [−3.40, −2.79]
Heterogeneity: Tau² = 3.08; Chi² = 17573.69, df = 129 (P < 0.00001); I² = 99%
Test for overall effect: Z = 19.89 (P < 0.00001)
−10 −5 0 5 10
Survivor Non-survivor

Figure 2. Forest plot of lactate dehydrogenase levels among survivors vs. non-survivors COVID-19 groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizonal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; SD — standard deviation.

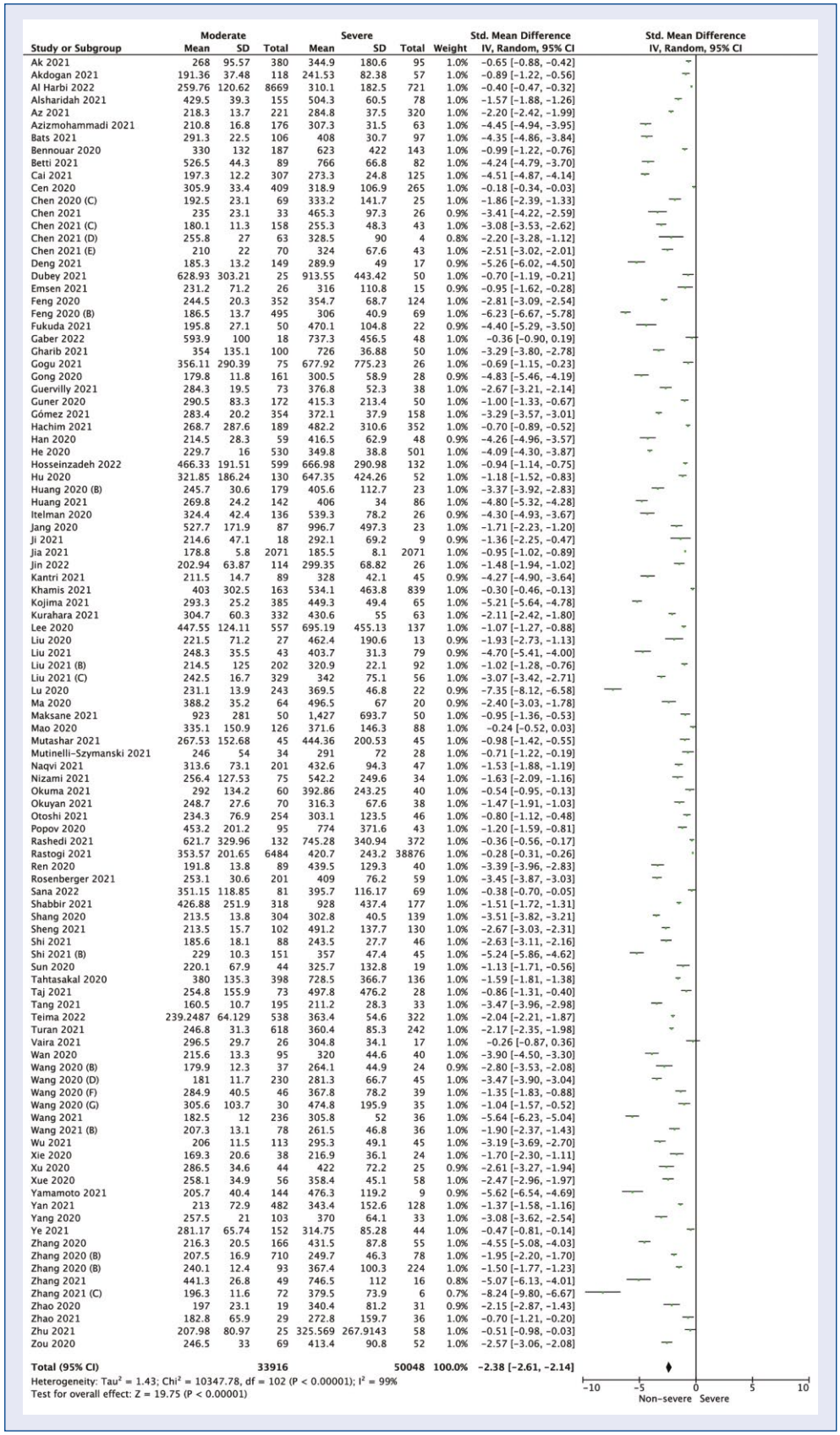

Figure 3. Forest plot of lactate dehydrogenase levels among moderate vs. severe COVID-19 groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizonal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; SD — standard deviation.

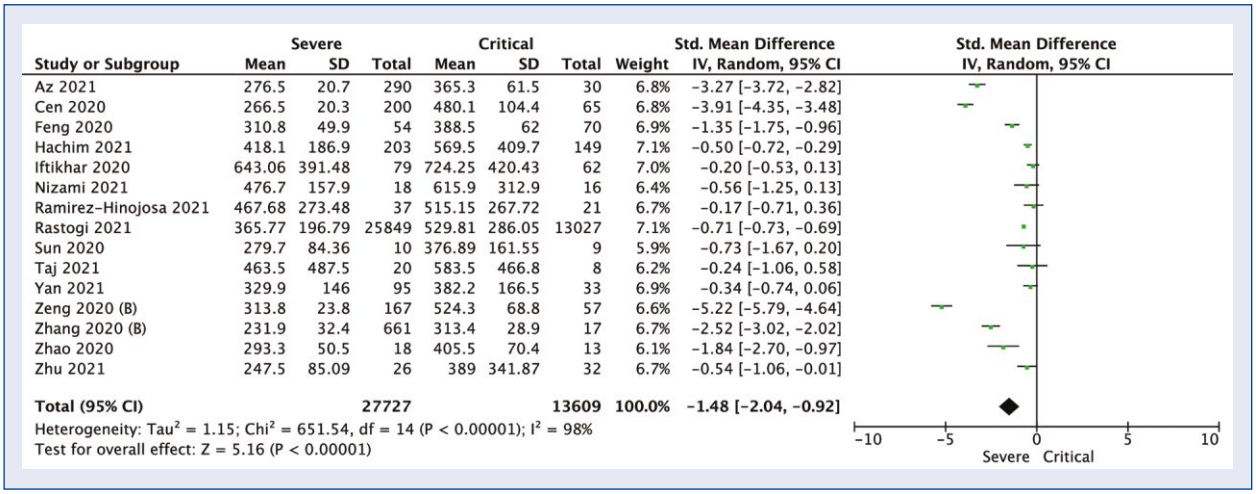

Figure 4. Forest plot of lactate dehydrogenase levels among severe vs. critical COVID-19 groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizonal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; SD — standard deviation.

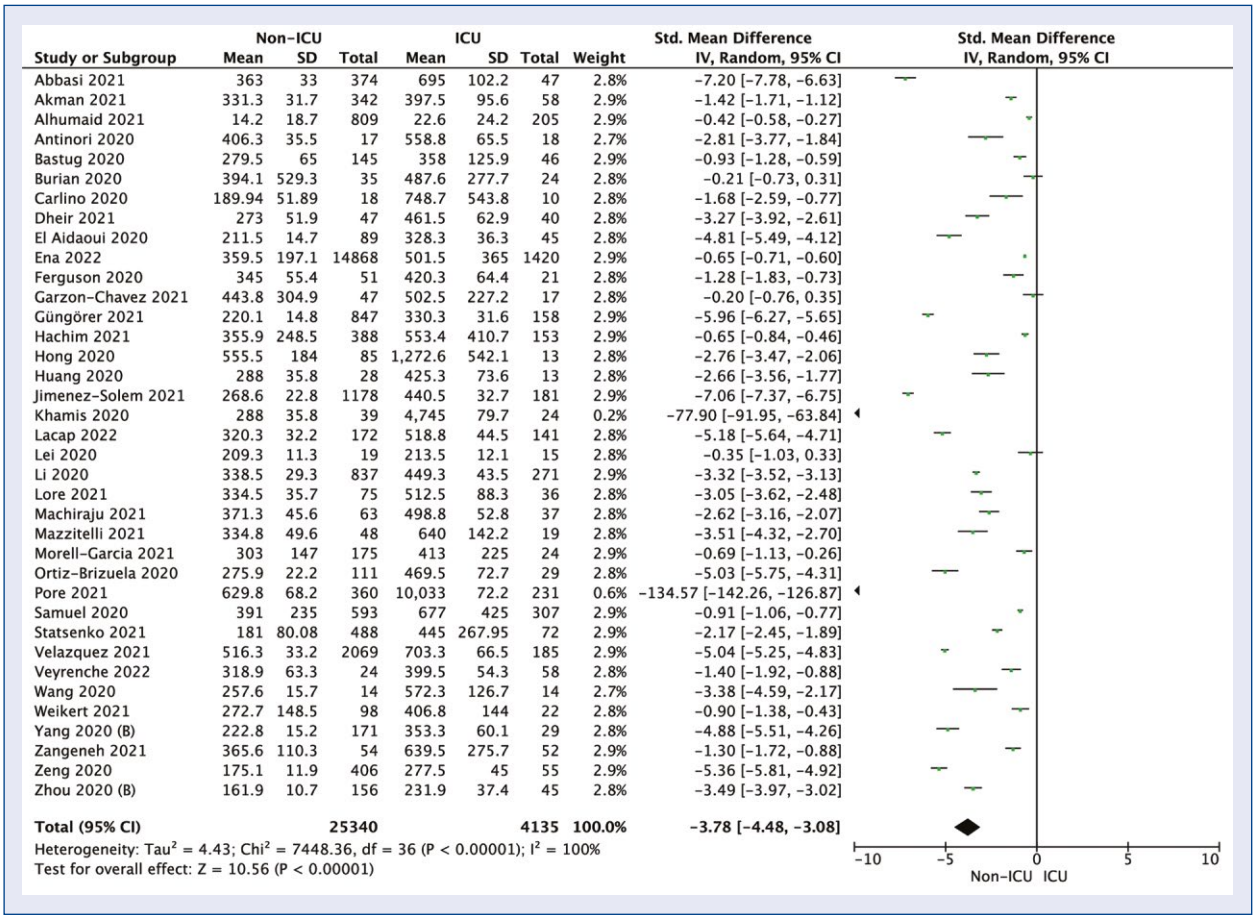

Figure 5. Forest plot of lactate dehydrogenase levels among non-intensive care unit (ICU) vs. ICU COVID-19 groups. The center of each square represents the weighted standard mean differences for individual trials, and the corresponding horizonal line stands for a 95% confidence interval (CI). The diamonds represent pooled results; SD — standard deviation.

Discussion

Lactate dehydrogenase plays a vital role in biochemical processes; it takes part in the interconversion of pyruvate, the final product of glycolysis to lactate without sufficient oxygen supply [29, 30]. Elevated LDH activity indicates a lack or deficiency of oxygen in biochemical processes, tissue oxygen deficiency, or multi-organ failure [31]. Increased LDH activity may be indicative of cellular damage, hypoxia or death. It should also be considered that elevated LDH activity may be associated with other conditions, including those associated with cardiac ischemia and pathological processes involving the lungs, renal cortex, liver, muscle, and red blood cells. Elevated LDH activity is also found in various malignant neoplasms.

Because of the clinical benefit of early identification of patients at risk for severe COVID-19, identification of markers of severe disease is of practical importance [32–33]. Several factors have been investigated to predict COVID-19 severity, including C-reactive protein, alanine aminotransferase, D-dimers, ferritin, Il-6, creatine kinase, aspartate aminotransferase, among others [34–36]. Recently, several studies have been undertaken to assess the utility of various markers indicative of severe COVID-19. One of these markers is elevated LDH activity. Several studies have shown elevated LDH activity in severe COVID-19 respiratory failure, COVID-19-related lung injury, and COVID-19-related multi-organ failure.

A problem that has been highlighted in studies investigating the association between COVID-19 severity and elevated LDH activity has been the small sample size and often retrospective nature of the analyses [22]. This meta-analysis addresses these methodological issues by including many new and extensive studies.

Herein, the usability of blood LDH determination in patients with COVID-19 was analyzed. 264 studies were included in a meta-analysis and changes in blood LDH concentrations were observed in patients with COVID-19 disease (**Suppl. material: [S1-S264]**). The clinical utility of blood LDH assay was then evaluated to differentiate the severity of SARS-CoV-2 infection.

This meta-analysis highlights the potential use of LDH as a biomarker for early determination of COVID-19 severity. LDH is released from cells following cell injury and death [37]. Often, this process is caused by hypoxia due to the disproportionate transfer of oxygen to the cells, the cause of which is, among others, SARS-CoV-2 infection.

The vast majority of studies evaluated in the meta-analysis presented a significant difference between LDH levels in patients with severe COVID-19 compared to patients who did not meet the criteria for severe disease. A study by Henry et al. [38] demonstrated a 6-fold increased likelihood of severe COVID-19 in patients with elevated LDH levels.

In the analyzed studies, elevated blood LDH levels were observed in a group of patients with severe COVID-19. LDH was a negative predictor of COVID-19 complications and death from the disease. The present study estimates that elevated blood LDH levels may be a biomarker that increases the likelihood of a severe course of COVID-19. These meta-analysis results indicate a strong relationship between elevated LDH activity with COVID-19 severity and increased patient mortality.

Determining the significance of LDH activity in the severity of COVID-19 is of clinical importance. However, given that many other biochemical parameters have been shown to be associated with mortality and severity of COVID-19, a multivariate analysis including a variety of biochemical parameters should be considered, which may further correlate with clinical course.

Limitations of the present analysis are due to the nature of the studies analyzed and the associated biases, mainly related to the retrospective nature of the analyses. The next step is a multivariate evaluation considering several biochemical parameters rather than a single biochemical indicator.

Conclusions

This meta-analysis showed that elevated LDH was associated with a poor outcome in COVID-19.

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Conflict of interest: None declared

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ORIGINAL ARTICLE

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First clinical experience of high-power ablation of atrial fibrillation with a novel contact force-sensing gold-tip catheter

Abdul Shokor Parwani[1, 2], Adrian Jayanata[1], Robin Kraft[1], Phillip Lacour[1, 2], Florian Blaschke[1, 2], Burkert Pieske[1, 2], Leif-Hendrik Boldt[1, 2]

[1]Department of Internal Medicine and Cardiology, Charité-Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany
[2]DZHK (German Center of Cardiovascular Research), partner site Berlin, Germany

Abstract

Background: *Contact force (CF)-sensing catheters are commonly used in the field of radiofrequency (RF) ablation to treat atrial fibrillation (AF). Increasing ablation power (e.g., 50 W) has been suggested as a method to reduce procedure times whilst creating safe and lasting lesions.*

Methods: *We report the first clinical evidence of a 50 W point-by-point RF ablation in 25 consecutive patients with symptomatic AF using a novel CF-sensing catheter with a gold tip (AlCath Force, BIOTRONIK). We collected and analyzed procedural and ablation parameters. The safety and efficacy of the catheter were evaluated.*

Results: *Altogether, 985 RF lesions in 25 patients were created with a mean number of 39.4 ± 16.3 lesions per patient. The total skin-to-skin procedure time was 116.1 ± 35.1 min, and the mean total area dose product was 10.9 ± 5.1 Gy*cm^2. The mean RF time per procedure was 13.2 ± 6.6 min. The mean RF time per lesion was 20.2 ± 8.4 s. The mean CF was 15.7 ± 7.6 g. We observed a mean force time integral of 274.7 ± 11.1 gs (range: 53 to 496 gs). Acute procedural success, defined as entrance and exit block in all pulmonary veins, could be obtained in all cases. No procedure- or device-related serious adverse events were observed. No audible steam pops occurred. Optical inspection of the catheter after the procedure showed neither charring nor clotting.*

Conclusions: *We provide the first evidence for the safety and efficacy of 50 W ablation using the AlCath Force gold-tip catheter. These data must be supported by a larger multi-center study.* (Cardiol J 2022; 29, 5: 759–765)

Key words: ablation, high power, contact force sensing, atrial fibrillation, gold-tip catheter

Introduction

The generation of transmural lesions for targeted ablation of atrial tachycardia circuits or substrate and pulmonary vein isolation (PVI) has been proven to be of high clinical value for the treatment of atrial rhythm disorders. Different energy forms are used to create these lesions, with radiofrequency (RF) energy being the most commonly used. To achieve transmural, lasting lesions, different settings of RF energy have been suggested with different relative contributions of the resistive or conductive heating phase [1].

Recently, high-power (≥ 50 W), short-duration (HPSD) RF ablation with irrigated contact force (CF) sensing catheters has been shown to be safe

Address for correspondence: Abdul Shokor Parwani, MD, Department of Internal Medicine and Cardiology, Charité-Universitätsmedizin Berlin, Campus Virchow Klinikum, Augustenburger Platz 1, 13353 Berlin, Germany, tel: +49 30 450 665410, e-mail: abdul.parwani@charite.de

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while reducing procedure and ablation times as compared to the traditional lower-power (e.g., 35 W), longer-duration ablation [2, 3]. Moreover, lesion width has been suggested to be increased as compared to traditional ablation techniques because a substantial fraction of the ablation time is represented by the resistive heating phase [4]. The improved thermal conductive properties of gold-tip catheters in comparison to platinum-iridium-tip catheters may also contribute to a favorable ablation effect. Ablation with CF sensing technology catheters has been linked to enhanced procedural safety and efficacy in traditional ablation settings [5–10].

We investigated a novel gold-tip irrigated ablation catheter with CF sensing (AlCath Force, BIOTRONIK) during PVI with 50 W in patients with paroxysmal and persistent atrial fibrillation (AF), with a focus on safety and efficacy.

Methods

Study population

The study enrolled all consecutive patients undergoing RF ablation of AF, in whom the AlCath Force Flux eXtra Gold catheter was used. Clinical, imaging, and procedural data were recorded. The AF type was categorized as paroxysmal when lasting < 1 week or persistent when lasting > 1 week and when electrical cardioversion was performed. The study protocol was approved by the Human Ethics Committee of the Charité-Universitätsmedizin Berlin (ethic application number: EA1/284/21) and is in accordance with the Declaration of Helsinki. All patients gave written informed consent.

Procedure and ablation settings

Prior to procedures, a transesophageal echocardiogram was performed in all patients to exclude atrial thrombus formation, and a transthoracic echocardiography was used to obtain measures of left atrial and ventricular function, as previously described [11]. Oral anticoagulation with vitamin K antagonists were continued, targeting an international normalized ratio of between 2 and 3. Direct oral anticoagulation was paused on the morning of the procedure and resumed after the procedure. During ablation, patients were sedated by using boluses of midazolam and a continuous infusion of propofol (1%). Fluoroscopy-guided transseptal puncture was performed and intravenous unfractionated heparin (initial bolus 100 U/kg) was administered with an intraprocedural activated clotting time between 300 and 400 s. An angiography of the left atrium (LA) was performed in angulations of RAO 30° and LAO 60° under rapid (200/min) ventricular stimulation prior to left atrial mapping and ablation.

The AcQMap (Acutus Medical) mapping system was used in all cases for three-dimensional (3D) electroanatomic mapping of the LA and pulmonary vein (PV) ostia. A decapolar circular mapping catheter (Map-IT, Access Point Technologies EP) was used to create a contact 3D-map of the LA and to document PV potentials. Two experienced operators performed the PVIs in our study cohort. In all cases a point-by-point wide antral circumferential ablation of all PVs was performed.

Lesions were generated using a 3.5 mm, open-tip, irrigated AlCath Force (BIOTRONIK) ablation catheter with a steerable sheath (Destino REACH 8.5 F, Oscor Medical). The catheter was continuously flushed with 2 mL/min of normal saline solution during mapping. Flush rate was increased to 15 mL/min during ablation with 1 s of pre-flushing and 2 s of post-flushing after ablation. RF energy was generated using an Ampere RF generator (Abbott) with a maximal temperature of 43°C at 50 W, including at the LA posterior wall.

Radiofrequency energy delivery was initiated at a stable CF between 10 and 30 g. We terminated RF energy delivery when the atrial electrograms diminished during ablation with a stable CF > 10 g. If atrial electrograms did not diminish sufficiently, RF ablation was terminated, regardless of the location, at a maximum force time integral (FTI) of 500 gs. The target inter-lesion distance was 4 mm.

After encircling the veins, entry and exit block were confirmed using a Biotronik circular mapping catheter (Map-IT, Access Point Technologies EP) by documenting any lack of vein potentials and failure to capture the atria while pacing inside the veins with high output (10 V, 2 ms).

Study outcomes

For each patient, we recorded pre-ablation clinical characteristics. For each ablation pulse, we obtained duration of RF application, impedance, power, CF, and FTI. All ablation parameters were analyzed and grouped according to the different atrial regions (**Suppl. Fig. 1**). Furthermore, the rate of attempts to isolate the PVs, the need for touch-up lesions, total RF ablation time, fluoroscopy data, and procedure time (skin-to-skin) were documented. Operators were instructed to report any occurrence of steam pops when perceived. Transthoracic echocardiography was performed after the procedure on the same day, to exclude pericardial effusion.

Table 1. Clinical characteristics by atrial fibrillation (AF) type given in mean ± standard deviation or number (%).

	Total	Paroxysmal AF	Persistent AF	P
Number of patients	25	18	7	–
Male	17 (68%)	13 (72%)	4 (57%)	0.49
Age [years]	67.5 ± 11.1	65.4 ± 11.8	72.9 ± 7.1	0.13
Body mass index [kg/m^2]	26.9 ± 4.0	26.1 ± 3.2	29.0 ± 5.1	0.09
EHRA-Score	2.4 ± 0.5	2.3 ± 0.5	2.7 ± 0.5	0.09
Cardiovascular risk factors				
Cardiovascular disease	9 (36%)	6 (33%)	3 (43%)	0.67
Prior stroke/TIA	3 (12%)	2 (11%)	1 (14%)	0.84
CHA_2DS_2-VASc	3.1 ± 1.6	2.8 ± 1.7	3.7 ± 1.1	0.21
Hypertension	21 (84%)	14 (78%)	7 (100%)	0.19
IDDM/NIDDM	3 (12%)	2 (11%)	1 (14%)	0.84
Echocardiography				
LVEF [%]	55.6 ± 11.8	54.9 ± 12.5	57.3 ± 10.5	0.66
LAVI [mL/m^2]	38.5 ± 16.0	37.6 ± 18.4	41.0 ± 7.5	0.67
Medication upon admission				
Beta-blocker	22 (88%)	16 (89%)	6 (86%)	0.84
Other antiarrhythmic drugs	2 (8%)	1 (6%)	1 (14%)	0.49
ACEI/AT1R-antagonist	18 (72%)	12 (67%)	6 (86%)	0.36
Oral anticoagulation	25 (100%)	25 (100%)	25 (100%)	–

ACEI — angiotensin converting enzyme inhibitor; AT1R — angiotensin-1-receptor; EHRA — European Heart Rhythm Association; LVEF — left ventricular ejection fraction; LAVI — left atrial volume index; (N)IDDM — (non-) insulin-dependent diabetes mellitus; TIA — transitory ischemic attack

To explore procedural associated safety, all patients were followed up 3 months after the procedure for symptoms suggestive of PV stenosis, phrenic nerve injury, late pericardial tamponade, or atrio-esophageal fistula. Esophageal temperature was not monitored in any of our cases.

Statistical analysis

Continuous variables are shown as mean ± standard deviation. Categorical variables are described as numbers and percentages. The statistical analysis was performed using t-tests or ANOVA for unpaired data as appropriate. A two-tailed p value of < 0.05 was used to indicate statistical significance.

Results

Patient characteristics

A total of 25 patients with symptomatic AF were consecutively included in this study. Patients' baseline clinical characteristics are given by AF type in Table 1. More than 1/3 of the patients were male. The mean age was 67.5 ± 11.1 years. Mean CHA_2DS_2-VASc score was 3.1 ± 1.6. Mean left atrial volume index was 38.5 ± 6.0 mL/m^2, and the mean left ventricular ejection fraction was 55.6 ± 11.8%. Most of the patients were treated with a beta-blocker and inhibitors of the renin–angiotensin–aldosterone system.

Procedural data

The procedure data are given in Table 2 and Figures 1 and 2. Total skin-to-skin procedure time was 116.1 ± 35.1 min with a mean RF time of 13.2 ± 6.6 min. Mean total area dose area product was 10.9 ± 5.1 Gy*cm^2. A total of 985 RF lesions were delivered with an average of 39.4 ± 16.3 lesions per patient. All lesions were applied with 50 W. Mean RF time per lesion was 20.2 ± 8.4 s, and the mean FTI was 274.7 ± 89.8 gs. An acute isolation of all PVs with proof of entrance and exit block was achieved in all patients. In the patients with paroxysmal AF (n = 18), this was achieved in 72% of patients with the initial completion of the circumferential ablation line (first-pass isolation). In the other patients, additional touch-up lesions were necessary to isolate all PVs. In patients with persistent AF (n = 7) additional touch-up lesions

Table 2. Procedural data by atrial fibrillation (AF) type given in mean ± standard deviation or number (%).

	Total	Paroxysmal AF	Persistent AF	P
Number of patients	25	18 (72%)	7 (28%)	–
Total skin-to-skin procedure time [min]	116.1 ± 35.1	116.4 ± 37.8	115.4 ± 29.7	0.95
RF time per procedure [min]	13.2 ± 6.6	13.8 ± 6.6	11.8 ± 6.9	0.53
Total area dose product [Gy*cm^2]	10.9 ± 9.1	10.1 ± 5.5	13.0 ± 15.5	0.49
Number of lesions per procedure	39.4 ± 16.3	40.6 ± 15.1	36.4 ± 20.2	0.58
First pass isolation	20 (80%)	13 (72%)	6 (86%)	0.67
Total number of lesions	985	730	255	–
RF time per lesion [s]	20.2 ± 8.4	20.4 ± 8.4	19.4 ± 8.4	0.36
Impedance drop per lesion [Ω]	8.8 ± 3.9	8.9 ± 4.0	8.6 ± 3.7	0.12
FTI per lesion [gs]	274.7 ± 89.8	273.1 ± 85.8	279.2 ± 100.7	0.20
Contact force per lesion [g]	15.7 ± 7.6	15.3 ± 7.3	16.6 ± 8.4	0.02

FTI — force time integral; RF — radiofrequency

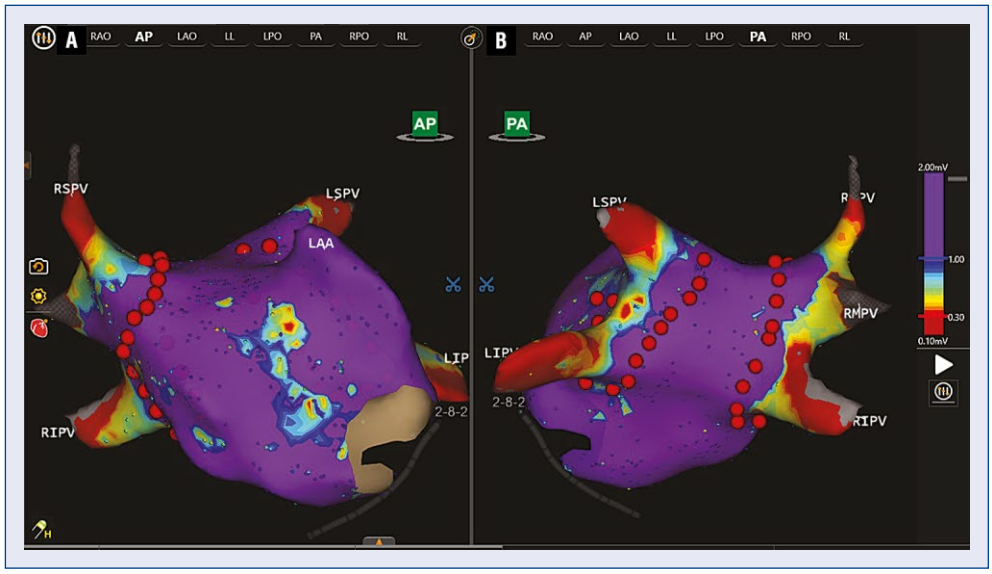

Figure 1. Three-dimensional electroanatomical map of the left atrium and location of point-by-point radiofrequency pulses (red dots) in anterior-posterior (AP) view (**A**) and in posterior-anterior (PA) view (**B**); LIPV — left inferior pulmonary vein; LSPV — left superior pulmonary vein; RIPV — right inferior pulmonary vein; RSPV — right superior pulmonary vein; LAA — left atrial appendage.

were needed in only 1 patient. Data regarding the number, location, and ablation parameters of touch-up lesions are depicted in **Supplementary Figures 2 and 3**.

Mean FTI at the anterior part of the LA was 289.9 ± 91.8 gs with a mean RF time per lesion of 22.1 ± 8.6 s and a mean CF of 15.1 ± 7.7 g. Mean FTI at the posterior part of the LA was 256.1 ± 89.7 gs ($p < 0.001$) with a mean RF time per lesion of 18.6 ± 8.0 s ($p < 0.001$) and a mean CF of 15.8 ± ± 7.4 g ($p = 0.22$). Most importantly, however, even high FTI values above 400 gs (8% of all lesions) with a mean RF duration of 21.7 ± 7.7 s and a mean CF of 22.0 ± 7.3 g did not lead to audible or tactile steam pops or adverse events (Fig. 3).

Safety and outcome

Overall, regarding the efficacy and safety, complete isolation of the PVs with entry and exit block was achieved in all patients without major adverse events. No audible steam pops occurred. No pericardial effusion was observed. At 3 months

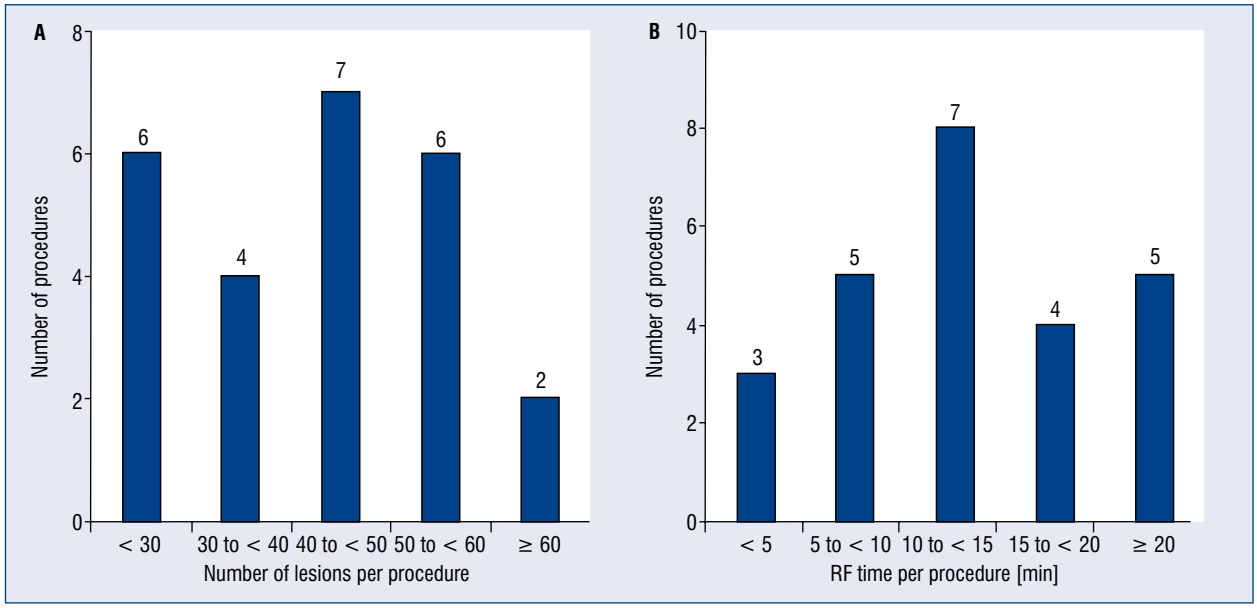

Figure 2. A, B. Procedural data; RF — radiofrequency.

of follow-up no additional serious adverse events occurred (e.g., stroke, atrio-esophageal fistula, symptomatic PV stenosis, phrenic nerve palsy).

Discussion

To the best of our knowledge, this is the first study reporting the safety and efficacy of an irrigated CF-sensing ablation catheter with a gold-tip electrode (AlCath Force) in a clinical setting of PVI with a 50 W ablation protocol. The steerable, irrigated, quadripolar AlCath Force catheter with an integrated force sensor and the Qubic Force device provide a novel system for measuring CF. It measures force in 3D using a single optical fiber. It can provide additional distal catheter flexibility, improving the application of the required force at challenging anatomies. Acute success, defined as entrance and exit block of all PVs, could be achieved in all cases in a short ablation time without any complications.

Pulmonary vein isolation is the cornerstone of catheter ablation of AF. Still, the most widely used ablation technique to isolate the PVs is point-by-point irrigated RF ablation guided by 3D electroanatomical mapping systems [12, 13]. CF sensing ablation catheters have been introduced to improve safety and generation of transmural lesions [14, 15]. Gold-electrodes were introduced because of the 4-fold higher thermal conductivity compared to platinum-iridium tip electrodes. This allows more efficient heat transmission with greater convective cooling, resulting in larger lesions. In a randomized trial, comparing non-contact gold-tip and platinum-iridium tip electrodes, Linhart et al. [16] were able to show that with irrigated gold-tip electrodes significantly more energy was delivered at a lower electrode tip temperature in patients undergoing PVI. Healy et al. [17] performed the BIOCONCEPT AlCath Force study, in which they showed the safety and efficacy of a gold-tip ablation catheter (AlCath Force) with CF sensing technology in 30 patients undergoing a PVI procedure with ablation power of 30 W. Recently it has been shown that ablation with high power and short duration produces wider but shallower lesions in a shorter ablation time [4, 18]. This is especially attractive in atrial ablation procedures due to the relatively thin atrial wall, which in most areas does not require deep, but rather wide, lesions to prevent gaps between lesions and collateral damage to surroundings structures, such as the esophagus.

In the present study our total RF and procedure times were further decreased as compared to our traditional "lower power" (i.e., 35 W) ablation approach and within the range reported for high-power ablations with platinum-iridium electrodes [2, 19]. On average, PVI could be achieved with 39 ± 16 RF applications per patient and a mean RF time per patient of 13.2 ± 6.6 min. These numbers are comparable to those reported for PVI with high-power protocols with platinum-iridium tip electrodes, and significantly shorter compared with conventional lower-power protocols [3, 19, 20].

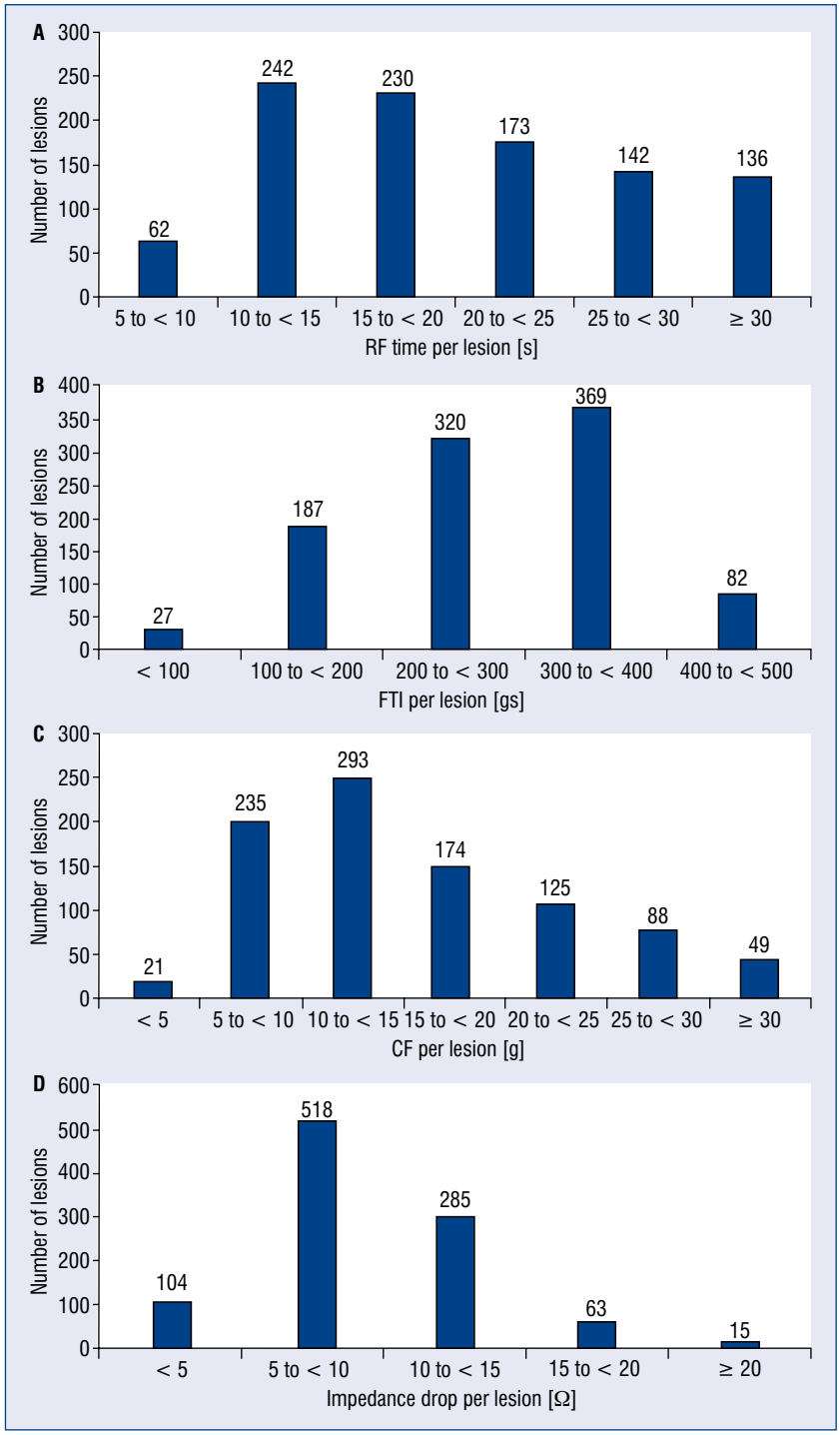

Figure 3. A–D. Ablation parameters; RF — radiofrequency; FTI — force time integral; CF — contact force.

Prediction of lesion size is an important aspect of safe and effective RF ablation, especially considering the known variability of myocardial wall thickness. FTI values above 400 gs have been recommended. Interestingly, in the present study, we observed FTI values between 53 and 496 gs with a mean FTI of 274.7 ± 89.8 gs. As reported by Winkle et al. [20], these results question the value and relevance of FTI as a target parameter when using a high-power technique. Physicians should be aware that FTI values during high-power ablation may be low despite creating an effective lesion. Traditional FTI cut-offs should be treated with caution in high-power ablation.

There were no acute procedure-related complications and no additional complications up to the 3-month follow-up visit. These data are encouraging and should prompt initiation of a larger, multi-center study.

Limitations of the study

This is a single-center observational study with a relatively low patient number, we did not randomize patients, and had no control group to compare the safety and efficacy of the ablation catheter.

Conclusions

We provide initial evidence for the safety and efficacy of a 50 W ablation strategy for PVI with the novel AlCath Force gold-tip catheter. However, large multicenter trials are necessary to further support our results.

Conflict of interest: None declared

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Silent cerebral infarcts in patients with atrial fibrillation: Clinical implications of an imaging-adjusted CHA_2DS_2-VASc score

John P. Bretzman[1], Andrew S. Tseng[2], Jonathan Graff-Radford[3], Hon-Chi Lee[2], Samuel J. Asirvatham[2], Michelle M. Mielke[3], David S. Knopman[3], Ronald C. Petersen[3], Clifford R. Jack Jr.[4], Prashanthi Vemuri[4], Alejandro A. Rabinstein[3], Christopher V. DeSimone[2]

[1]Department of Internal Medicine, Mayo Clinic, Rochester, MN, United States
[2]Department of Cardiovascular Medicine, Mayo Clinic, Rochester, MN, United States
[3]Department of Neurology, Mayo Clinic, Rochester, MN, United States
[4]Department of Radiology, Mayo Clinic, Rochester, MN, United States

Abstract

Background: *The CHA_2DS_2-VASc score does not include silent infarcts on neuroimaging in stroke risk estimation for patients with atrial fibrillation (AF). The inclusion of silent infarcts into CHA_2DS_2-VASc scoring and its impact on stroke prophylaxis recommendations in patients with AF has not been previously studied. The present study sought to quantify the prevalence of silent infarcts in patients with AF and describe potential changes in management based on magnetic resonance imaging (MRI) findings.*

Methods: *Participants from the Mayo Clinic Study of Aging with AF and brain MRI were included. Silent infarcts were identified. "Standard" CHA_2DS_2-VASc scores were calculated for each subject based on clinical history alone and "imaging-adjusted" CHA_2DS_2-VASc scores based on evidence of cerebral infarction on MRI. Standard and imaging-adjusted scores were compared.*

Results: *One hundred and forty-seven participants (average age 77, 28% female) were identified with AF, MRI, and no clinical history of stroke. Overall, 41 (28%) patients had silent infarcts on MRI, corresponding with a 2-point increase in CHA_2DS_2-VASc score. Of these participants, only 39% (16/41) with silent infarct were on anticoagulation despite having standard CHA_2DS_2-VASc scores supportive of anticoagulation. After incorporating silent infarcts, 13% (19/147) would have an indication for periprocedural bridging compared to 0.6% (1/147) at baseline.*

Conclusions: *Incorporation of silent infarcts into the CHA_2DS_2-VASc score may change the risk--benefit ratio of anticoagulation. It may also increase the number of patients who would benefit from periprocedural bridging. Future research should examine whether an anticoagulation strategy based on imaging-adjusted CHA_2DS_2-VASc scores could result in a greater reduction of stroke and cognitive decline.* (Cardiol J 2022; 29, 5: 766–772)

Key words: anticoagulation, atrial fibrillation, bridging, magnetic resonance imaging, silent infarct

Address for correspondence: Christopher V. DeSimone, MD, PhD, Ass. Prof., Department of Cardiovascular Medicine, Mayo Clinic College of Medicine, 200 1st St SW, Rochester, MN 55905, United States, tel: (507) 284-2511, e-mail: desimone.christopher@mayo.edu

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Introduction

In the United States alone, over 5.2 million people have a diagnosis of atrial fibrillation (AF), and this number is expected to triple over the next three decades [1]. AF increases the risk of ischemic stroke, and antithrombotic agents are recommended for high-risk patients. The 2019 American College of Cardiology/American Heart Association (ACC/AHA) AF guidelines recommend using the CHA_2DS_2-VASc score to estimate annual stroke risk and to determine the need for anticoagulation. Anticoagulation is a class IA recommendation for men with a score of ≥ 2, and women with a score ≥ 3. Anticoagulation is a class IIb recommendation for a score of 1 in men and 2 in women [2].

The CHA_2DS_2-VASc scoring system is based on studies that define stroke clinically (sudden onset neurologic deficit lasting > 24 h diagnosed by a neurologist for stroke or < 24 h for transient ischemic attack [TIA]) [3]. However, it is also recognized that there are patients with computed tomography (CT) or magnetic resonance imaging (MRI) evidence of cerebral infarction without any previous clinical manifestations. These are termed "silent infarcts" and are not accounted for in current stroke risk estimation criteria. The prevalence of silent infarct in AF is estimated to be between 14% [4, 5] and 30% [6, 7] and is higher in patients with AF compared to those without [8, 9]. Silent infarction is associated with future clinical infarction and cognitive impairment [6, 10–12].

The impact of including silent infarcts on neuroimaging into the CHA_2DS_2-VASc scoring system and stroke prophylaxis recommendations in patients with AF has not been previously studied. To evaluate the clinical implications, a cohort was utilized from the population-based Mayo Clinic Study of Aging (MCSA). This database is uniquely suited to study this question due to the routine use of brain MRI. In this study, it was sought to quantify the prevalence of silent infarcts in patients with AF and describe potential changes in management based on MRI findings.

Methods

Study design

Participants were enrolled in the MCSA, a prospective, longitudinal, population-based study of aging and cognitive decline that began enrolling patients in 2004. The MCSA study design has been previously published [13]. In the MCSA, residents of Olmsted County, Minnesota were identified and randomly sampled in an age- and sex-stratified manner using the Rochester Epidemiology Project medical records-linkage system [14]. Participants without contraindications (i.e., pacemaker or other implanted devices) were invited to undergo brain MRI imaging at the time of enrollment and at various points throughout the study. For the present study, the first MRI available for each participant was used. The MCSA and associated studies were approved by the Mayo Clinic and Olmsted Medical Center Institutional Review Boards. Written informed consent was obtained from all participants prior to study enrollment.

Clinical data retrieval

Clinical data were abstracted by a nurse from the detailed medical records included in the medical records–linkage system from the Rochester Epidemiology Project [14]. Diagnosis of AF was based on physician diagnosis, electrocardiographic evidence of AF, and/or treatment for AF. Using this method, patients with postoperative AF were included. Infarcts were graded on two-dimensional FLAIR MRI that was co-registered with magnetization-prepared rapid gradient-echo T1 MRI. The full details of infarct grading have been previously published [15]. All possible infarcts were initially identified by trained image analysts and subsequently confirmed by a vascular neurologist (J.G.R.) who was blinded to all clinical information [15].

Outcomes

For the main analysis, CHA_2DS_2-VASc scores were calculated for each participant as per the usual method, only counting points for clinical history of stroke ("standard" CHA_2DS_2-VASc). For this study, a second "imaging-adjusted" CHA_2DS_2--VASc score was also calculated, for which stroke was defined as evidence of infarct on MRI regardless of clinical diagnosis (i.e., including radiologically documented infarctions that may have been clinically silent or not previously clinically diagnosed).

Standard and imaging-adjusted scores were compared for outcomes of interest. Patients with an increase in score from their standard to imaging--adjusted score were identified. The 2019 ACC/AHA AF guidelines were used to determine if a change in management would be indicated for patients based on their imaging-adjusted CHA_2DS_2-VASc score [2]. The 2017 ACC periprocedural anticoagulation guidelines were used to determine if a change in bridging anticoagulation would be indicated based on imaging-adjusted scores [16]. Bridging antico-

Table 1. Baseline characteristics.

CHA_2DS_2-VASc criteria	Overall cohort (n = 147)	Silent infarct	
		Present (n = 41)	Absent (n = 106)
Age, mean ± SD	77 ± 10	82 ± 6	75 ± 10
Female	41 (28%)	9 (22%)	32 (30%)
CHF	39 (27%)	16 (39%)	23 (22%)
Hypertension	121 (82%)	39 (95%)	82 (77%)
Stroke	0 (0%)	0 (0%)	0 (0%)
TIA	13 (9%)	0 (%)	13 (12%)
CAD	71 (48%)	31 (76%)	40 (38%)
PAD	14 (10%)	2 (5%)	12 (11%)
Diabetes mellitus	34 (23%)	8 (20%)	26 (25%)

CAD — coronary artery disease; CHF — congestive heart failure; PAD — peripheral arterial disease; SD — standard deviation; TIA — transient ischemic attack

agulation was defined as the periprocedural use of full-dose parenteral anticoagulants.

Statistical analysis

Descriptive statistics were used to calculate central tendencies, measures of spread, and prevalence for the current cohort. Mean age with standard deviation, and prevalence of each of the CHA_2DS_2-VASc criteria (age, sex, congestive heart failure, hypertension, stroke/TIA, vascular disease, and diabetes mellitus) were calculated. The prevalence of silent infarcts for each standard CHA_2DS_2-VASc score was determined. Lastly, the number of participants on anticoagulation, acetylsalicylic acid, and dual antiplatelets was quantified. Data analysis was performed using BlueSky Statistics Version 7.20 (BlueSky Statistics, Chicago, Illinois).

Results

Baseline characteristics and antithrombotic regimen of the study cohorts

The present cohort was developed by including all MCSA participants with AF, brain MRI at the time of enrollment, and sufficient data available for CHA_2DS_2-VASc score calculation. Those with a history of clinically apparent stroke were excluded so that those with silent stroke could be identified. Overall, 147 patients were included in the study. Baseline characteristics of the initial cohort are summarized in Table 1. The cohort was separated into two groups — those with silent infarct (n = 41) and those without silent infarct (n = 106). This design is visually depicted in Figure 1. Among the 147 participants, 41 (28%) had evidence of silent infarct on MRI, which resulted in an increase of their CHA_2DS_2-VASc scores by 2 points. CHA_2DS_2-VASc scores prior to and after imaging adjustment is visually depicted in Figure 2. The rate of anticoagulation was 35% (51/147), which is 37% (51/137) of those with a standard CHA_2DS_2-VASc score high enough to warrant anticoagulation. Antiplatelet use included acetylsalicylic acid alone in 47%, dual antiplatelet therapy in 7%, and 11% were on neither anticoagulation nor antiplatelet agents. Of the 52 participants on anticoagulation, 50 were on warfarin, 1 was on a heparin product, and 1 was on an unspecified anticoagulant.

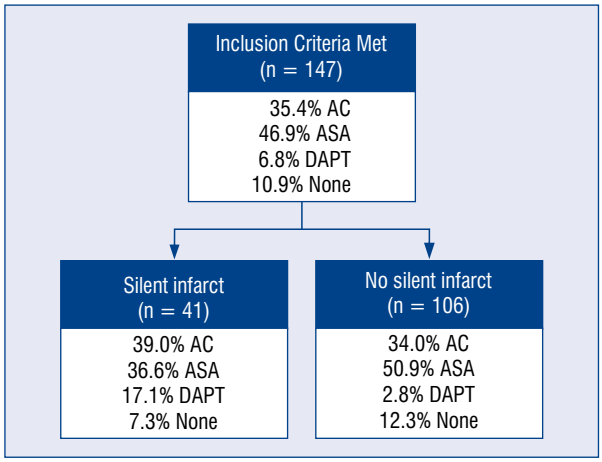

Figure 1. Study design and summary of results. 147 participants with atrial fibrillation, magnetic resonance imaging upon enrollment, and no clinical history of stroke were identified. 41/147 had silent infarct. Notably, only 39% were anticoagulated despite all having an indication for anticoagulation; AC — anticoagulation; ASA — acetylsalicylic acid; DAPT — dual antiplatelet therapy.

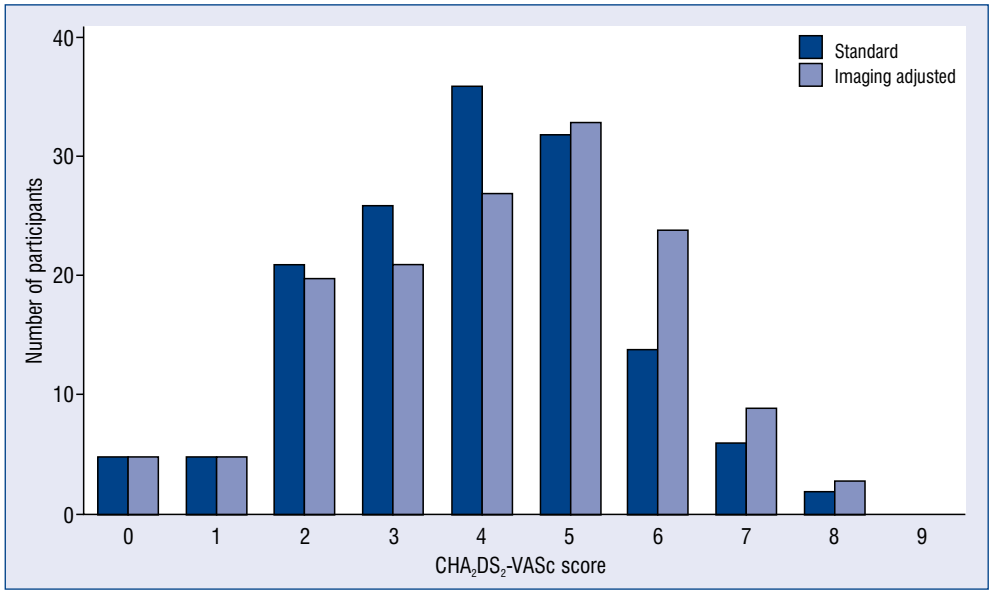

Figure 2. Change from standard to image adjusted CHA_2DS_2-VASc score. After incorporating imaging evidence of silent infarct, many participants had an increase in CHA_2DS_2-VASc score, causing a shift to the right.

Impact on stroke prophylaxis management in patients with silent infarcts

None of the patients with silent infarct (n = 41) had a standard CHA_2DS_2-VASc < 2. Thus, after adjustment for imaging findings, no patients would have had a new indication for anticoagulation based on current AF management guidelines. However, among the 41 patients with silent brain infarction, only 39% (16/41) were anticoagulated despite all of them having a standard CHA_2DS_2-VASc score supporting anticoagulation. This rate of anticoagulation was no different than those without silent infarct (36/106, 34%, p = 0.58).

Impact on bridging anticoagulation management in patients with silent infarcts

Of the 147 patients analyzed for silent infarct, only one participant had an indication for bridging based on their standard CHA_2DS_2-VASc score. After calculation of imaging adjusted CHA_2DS_2-VASc scores, anticoagulation would have been indicated in 19/147 (13%) participants after imaging adjustment. This indication for bridging would have been a new indication for 18/147 (12%). In other words, for those participants with silent infarct on MRI, 44% (18/41) had a new indication for periprocedural bridging. All of the present findings are summarized in the Figure 3.

Discussion

Main findings

The impact of imaging-adjusted CHA_2DS_2--VASc scores on chronic and periprocedural anticoagulation recommendations was evaluated, and it was found that: 1) 28% of participants with AF had evidence of cerebral infarct despite no clinical history of stroke, 2) only 39% of participants who had silent infarct were on anticoagulation despite all of them having a standard CHA_2DS_2-VASc score supporting the use of anticoagulation, and 3) use of image-adjusted CHA_2DS_2-VASc scores would have led to 12% of our cohort having a new indication for peri-procedural bridging.

Clinical relevance

Although silent infarcts may seem inconsequential due to lack of overt focal symptoms, silent infarcts are clinically important. Previous studies have demonstrated increased risk of dementia and future risk of clinically apparent strokes in patients with silent infarcts on imaging [6, 10–12]. Recognizing the clinical ramifications of these silent infarcts should affect clinical management. Yet, current scoring systems used to decide whether to prescribe anticoagulation do not take silent infarcts on neuroimaging into consideration.

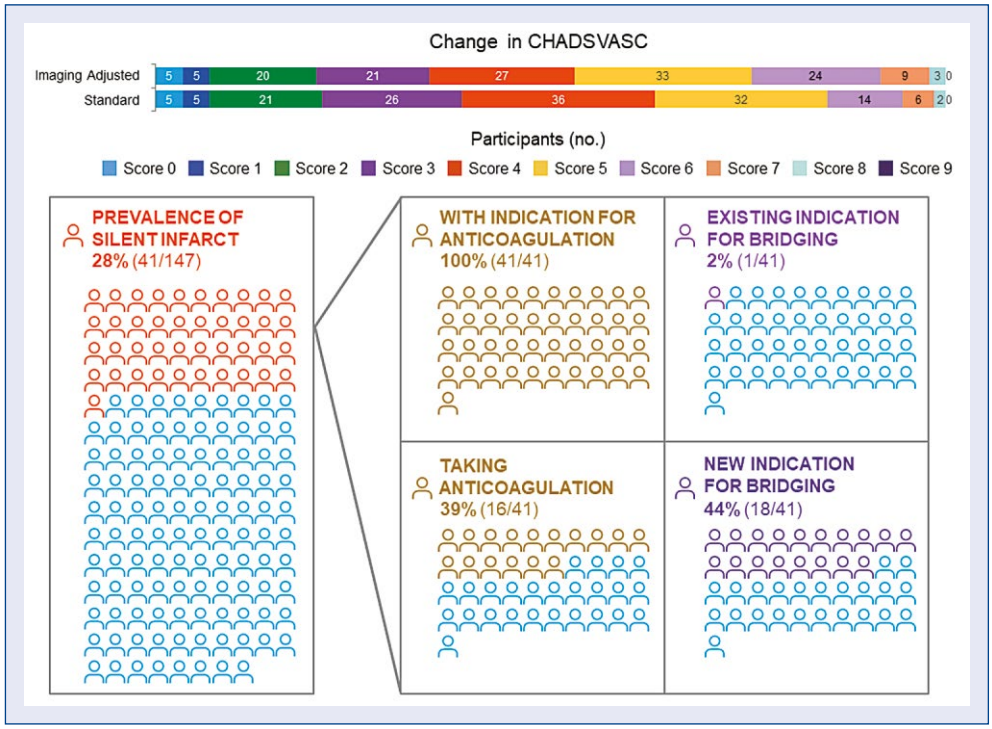

Figure 3. The present study found that the prevalence of silent infarct in patients with atrial fibrillation is 28%. 39% of these participants were anticoagulated, despite all of them having an indication for anticoagulation. After incorporating silent infarct into stroke risk estimation, 44% of those with silent stroke had a new indication for periprocedural bridging. The top of the figure shows how CHA_2DS_2-VASc scores change after imaging adjustment.

Prevalence of silent infarct

Silent stroke is commonly encountered in the clinical setting as an incidental discovery when head imaging is obtained for other purposes. There is an increased prevalence of silent stroke in patients with AF when compared to the general population [8, 9]. In the current cohort, a substantial proportion (28%) of patients with AF had silent stroke on brain MRI. Other studies report varying prevalence of silent stroke in AF. Older studies such as the SPINAF trial (1995) and EAFT study group (1996) showed silent stroke prevalence of 14.7% and 14%, respectively based on CT findings [4, 5]. Other studies using MRI have estimated the risk of stroke to be similar to our data, at 28.3% [7]. The differences are likely due to increased sensitivity of MRI over CT imaging in detecting small ischemic lesions [17, 18].

Impact on anticoagulation management

Given the high prevalence of silent stroke in patients with AF, the benefit of anticoagulation is likely underestimated by CHA_2DS_2-VASc scoring. If silent infarcts are accounted for, 28% of the present study participants would have an increase in their CHA_2DS_2-VASc scores by 2 points, increasing their estimated annual risk of stroke. Only 39% of those with silent infarct were on anticoagulation, and the rate of anticoagulation in those with a prior history of stroke was only 42%. However, these low rates are similar to previously reported rates of anticoagulation for patients with AF with an indication for anticoagulation [19].

The reason for low anticoagulation rates despite an indication for anticoagulation is unclear. It is possible that many patients had increased risk of bleeding, or some may have had a lower estimation of stroke risk based on the older $CHADS_2$ score. Regardless, if imaging-adjusted CHA_2DS_2-VASc scores are used, patients with silent infarcts would have a 2-point increase, shifting the risk-benefit ratio even further towards anticoagulation. In other words, while many patients in the present cohort had a baseline indication for anticoagulation by CHA_2DS_2-VASc score regardless of brain imaging, the presence of silent infarct on brain imaging may prompt further consideration of anticoagulation given the increased stroke risk from the presence of silent infarct.

Impact on bridging anticoagulation management

Bridging anticoagulation is an important management concern in those with AF, and the decision to bridge with heparin prior to procedures is guided by the CHA_2DS_2-VASc score as well. Per the 2017 ACC guidelines on periprocedural anticoagulation, bridging prior to or after procedures is dependent on the risk of thrombotic events. Patients are categorized into high, moderate, or low risk groups. High risk corresponds to a CHA_2DS_2-VASc of 7 or greater, moderate corresponds to a score of 5–6, and low risk is a score of 4 or less [16]. Using the imaging-adjusted CHA_2DS_2-VASc score, bridging anticoagulation in the periprocedural period would have been indicated for 18/147 (12%) participants who would not have met the 2017 ACC guidelines criteria for bridging based on their standard CHA_2DS_2-VASc score. In other words, 18 of the 41 (44%) participants with silent infarct had a new indication for bridging.

Limitations of the study

This study is limited since a database with previously extracted data was used. Therefore, there was limited insight into details such as the rationale for choice of anticoagulant, decision not to anticoagulate, and the chronicity of the AF. The average age of the cohort was 77 years, and 28% were female. Although previous studies have demonstrated higher prevalence of AF with increasing age and higher prevalence in men compared to women in all age groups, the ratio of women to men appears to be lower than what other population-based studies estimate [20]. The advanced age of the present cohort determined that many patients had a standard CHA_2DS_2-VASc score of 2 based on age alone. Thus, the clinical implications of using an imaging-adjusted CHA_2DS_2-VASc score may be greater in a younger cohort, because more individuals would start with a lower standard CHA_2DS_2-VASc score and cross the threshold for indication of anticoagulation after imaging adjustment. Additionally, while the study was population-based, the population was predominantly white and, therefore, future studies with more diverse populations are needed. Another limitation is that some patients with difficult-to-control AF undergo atrioventricular nodal ablation with pacemaker placement, which may predispose to stroke. However, this population was unable to be captured in the current study due to the incompatibility with MRI.

Conclusions

In this population-based cross-sectional study, 28% of patients with AF had evidence of infarct on MRI despite not having clinical history of stroke (referred to as silent infarct). Only 39% of the patients with silent infarct were on anticoagulation, despite already having a baseline CHA_2DS_2-VASc score ≥ 2 points. If silent brain infarct was included in the definition of stroke, a significant subset of patients would have a 2-point increase in their CHA_2DS_2-VASc score. Such an adjustment would substantially increase their estimated annual stroke risk and would more strongly support the use of anticoagulation as the risk-benefit ratio shifts in favor of anticoagulation. Similarly, use of imaging-adjusted CHA_2DS_2-VASc scores would have major implications on which patients receive periprocedural bridging. Based on the present findings, the value of anticoagulation based on imaging-adjusted CHA_2DS_2-VASc scores should be formally examined in future longitudinal studies.

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Conflict of interest: Michelle M. Mielke has consulted for Biogen and Brain Protection Company. David S. Knopman serves on a Data Safety Monitoring Board for the DIAN study. He serves on a Data Safety monitoring Board for a tau therapeutic for Biogen but receives no personal compensation. He is an investigator in clinical trials sponsored by Biogen, Lilly Pharmaceuticals and the University of Southern California. He has served as a consultant for Roche, Samus Therapeutics, Third Rock and Alzeca Biosciences but receives no personal compensation. He receives funding from the NIH. Clifford R. Jack Jr. serves on an independent data monitoring board for Roche, has served as a speaker for Eisai, and consulted for Biogen, but he receives no personal compensation from any commercial entity. He receives research support from

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Optimal surgical timing after post-infarction ventricular septal rupture

Juan Diego Sánchez Vega[1], Gonzalo Luis Alonso Salinas[1], José María Viéitez Florez[1], Albert Ariza Solé[2], Esteban López de Sá[3], Ricardo Sanz-Ruiz[4], Virginia Burgos Palacios[5], Sergio Raposeiras Roubin[6], Susana Gómez Varela[7], Juan Sanchís Forés[8], Lorenzo Silva Melchor[9], Xurxo Martínez-Seara[10], Lorena Malagón López[11], Ana Viana Tejedor[12], Miguel Corbí Pascual[13], José Luis Zamorano Gómez[1], Marcelo Sanmartín Fernández[1]; for the CIVIAM Study Investigators*

[1]Department of Cardiology, Hospital Universitario Ramón y Cajal, IRYCIS, CIBERCV, Madrid, Spain; [2]Department of Cardiology, Hospital Universitari de Bellvitge, Hospitalet de Llobregat, Spain; [3]Department of Cardiology, Hospital Universitario La Paz, IDIPAZ, Madrid, Spain; [4]Department of Cardiology, Hospital Universitario Gregorio Marañón, Madrid, Spain; [5]Department of Cardiology, Hospital Universitario Marqués de Valdecilla, Santander, Spain; [6]Department of Cardiology, Hospital Universitario Álvaro Cunqueiro, Vigo, Spain; [7]Department of Cardiology, Hospital Universitario de Cruces, Baracaldo, Sapin; [8]Department of Cardiology, Hospital Clínico Universitario de Valencia, INCLIVA, Universidad de Valencia, CIBERCV, Valencia, Spain; [9]Department of Cardiology, Hospital Universitario Puerta de Hierro, Majadahonda, Spain; [10]Department of Cardiology, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain; [11]Department of Cardiology, Complejo Hospitalario de Navarra, Pamplona, Spain; [12]Department of Cardiology, Hospital Clínico San Carlos, Instituto de Investigación Sanitaria Clínico San Carlos, Madrid, Spain; [13]Department of Cardiology, Complejo Hospitalario Universitario de Albacete, Albacete, Spain

Abstract

Background: *Ventricular septal rupture (VSR) following acute myocardial infarction (AMI) is a dangerous condition. Surgical VSR closure is the definitive therapy, but there is controversy regarding the surgical timing and the bridging therapy between diagnosis and intervention. The objective of this study is to analyze the ideal time of surgical repair and to establish the contribution of mechanical circulatory support (MCS) devices on the prognosis.*

Methods: *We designed an observational, retrospective, multicenter study, selecting all consecutive patients with post-AMI VSR between January 1, 2008 and December 31, 2018, with non-exclusion criteria. The main objective of this study was to analyze the optimal timing for surgical repair of post-AMI VSR. Secondary endpoints were to determine which factors could influence mortality in the patients of the surgical group.*

Results: *A total of 141 patients were included. We identified lower mortality rates with an odds ratio of 0.3 (0.1–0.9) in patients operated on from day 4 compared with the surgical mortality in the first 24 hours after VSR diagnosis. The use of MCS was more frequent in patients treated with surgery, particularly for intra-aortic balloon pump (IABP; 79.6% vs. 37.8%, $p < 0.001$), but also for veno-arterial extracorporeal membrane oxygenation (VA-ECMO; 18.2% vs. 6.4%, $p = 0.134$). Total mortality was 91.5% for conservative management and 52.3% with surgical repair ($p < 0.001$).*

Conclusions: *In our study, we observed that the lowest mortality rates in patients with surgical repair of post-AMI VSR were observed in patients operated on from day 4 after diagnosis of VSR, compared to earlier interventions.* (Cardiol J 2022; 29, 5: 773–781)

Key words: ventricular septal rupture, acute myocardial infarction, cardiogenic shock, mechanical complications, extracorporeal membrane oxygenation

Address for correspondence: Dr. Marcelo Sanmartín Fernández, Department of Cardiology, Hospital Universitario Ramón y Cajal, Carretera Colmenar Viejo, km. 9, 100, 28034, Madrid, Spain, tel/fax: +34 913368515, e-mail: msanfer@me.com

**CIVIAM study: Comunicación InterVentricular en Infarto Agudo de Miocardio (Ventricular septal rupture in acute myocardial infarction).*

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Introduction

Ventricular septal rupture (VSR) following an acute myocardial infarction (AMI) is a rare but extremely dangerous condition [1, 2]. Since the beginning of the percutaneous reperfusion era, the incidence of VSR has decreased to less than 1%. However, no significant change in mortality has been observed, remaining dramatically high, with rates between 38% and 88% in the first 30 days [3–5]. Furthermore, these mortality rates have not shown meaningful changes in recent studies [6–8]. In addition, the recent COVID-19 pandemic has led to delays in health care, which has resulted in an increase in the incidence of mechanical complications after a myocardial infarction, with high mortality rates [9].

Ventricular septal rupture most frequently leads to a quick instauration of cardiogenic shock and multiorgan failure, making it difficult to analyze different treatment strategies, and no data from randomized trials are available [10]. Despite increased use of mechanical circulatory support (MCS) in recent years, there is still controversy on the timing, management of complications, and the optimal role of these devices in VSR patients [11].

Moreover, although VSR closure is considered the definitive therapy for the majority of patients, the ideal surgical timing and the optimal bridging therapy between diagnosis and intervention still represent important gaps in knowledge in this difficult scenario [12–18]. Our group recently published a trend towards a decrease in mortality in the last years, without clarifying which factors correlated with better survival [14].

Accordingly, we analyzed a large multicenter database to gain new insight on the adequate surgical timing as a definitive therapy and try to establish the contribution of MCS devices to the overall prognosis of VSR patients.

Methods

Study design, population, and data collection

We performed an observational retrospective study, recruiting all consecutive patients with post-AMI VSR from 13 tertiary public centers in our country. The study was approved by institutional review boards, and we selected consecutive patients with post-AMI VSR between January 1, 2008 and December 31, 2018, from each local database with non-exclusion criteria. An invitation was sent to 13 tertiary hospitals in Spain with available organized reperfusion networks located in different geographical regions. In comparison to our previous analyses, we added 2 centers to our study group and 21 patients to obtain a more robust database [14].

Participating hospitals had either on-site cardiac surgery or easy access to rapid transfer of patients with mechanical complications and access to electronic medical history, from which data of the event and follow-up were obtained. The diagnosis of VSR was obtained by Doppler echocardiography or cardiac catheterization. A database for analysis was created with the information available from the electronic registries and specific individual databases of the cardiovascular intensive care unit. The decision to undergo surgery, percutaneous closure, or conservative treatment was defined by each center or attending multidisciplinary team.

Clinical endpoints

The main objective of the present analysis was to explore the optimal timing for surgical repair of post-AMI VSR. We specifically observed in hospital and 1-year mortality of the patients included depending on the days between diagnosis and surgery.

Secondary endpoints were to determine which factors could influence mortality, comparing the surgical repair group and the medical treatment group, and specifically in the patients of the surgical group.

Statistical analysis

Patient characteristics are summarized with continuous variables expressed as means (standard deviation), or median (interquartile range [IQR]) if with non-normal distribution, and categorical variables are presented as frequencies and percentages.

As a first step, we performed a univariate analysis. We compared numerical data in both groups using the T-test for continuous normal distribution variables and the Wilcoxon test for those with a skewed distribution. Categorical dichotomous variables were compared using the χ^2 test or Fisher's exact test when appropriate. Categorical non-dichotomous variables were compared using the ANOVA test. Secondly, we performed multivariate analysis with logistic regression. On the multivariate analysis model, all statistically significant variables identified in univariate analysis were included. To avoid overestimating the survival rate in both groups, we excluded from our analysis patients who underwent cardiac transplant (1 patient in the surgical group and 5 in the conservative group, leaving a total of 135 patients for this analysis).

Table 1. Baseline characteristics.

Variable	Surgery (n = 88)	Conservative (n = 47)	P
Age [years]*	71.1 (65.1–76.7)	81.6 (77.5–83.9)	< 0.001
Female sex	34 (38.6%)	23 (48.9%)	0.248
Arterial hypertension	52 (59.1%)	35 (74.5%)	0.075
Diabetes	34 (38.6%)	15 (31.9%)	0.439
BMI [kg/m^2]	26.8; 3.8	27.1; 4.4	0.690
BMI ≥ 30	15 (21.4%)	7 (25.0%)	0.702
Smoker (past or current)	34 (38.6%)	16 (33.0%)	0.730
GFR [mL/min]	54.8; 21.9	47.9; 21.6	0.090
Previous STEMI	4 (4.6%)	1 (2.1%)	0.479
Previous NSTEMI	2 (2.3%)	3 (6.4%)	0.228
Previous PCI	4 (4.6%)	3 (6.4%)	0.646
Previous CABG	0 (0%)	2 (4.3%)	0.051
Peripheral artery disease	5 (5.7%)	4 (8.7%)	0.508
Previous stroke	3 (3.4%)	1 (2.2%)	0.690
Charlson score*	4 (3–6)	5.5 (4–7)	0.015
Euroscore II*	13.4 (7.6–25.9)	20.4 (9.9–33.7)	0.093

*Non-normal distribution. The data are expressed as mean ± standard deviation and median [interquartile range] or number (percentage). BMI — body mass index; CABG — coronary artery bypass grafting; GFR — glomerular filtration rate; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; STEMI — ST-segment elevation myocardial infarction

To calculate the optimal time for surgery, the incidence of in-hospital mortality was analyzed for each waiting day of the total 89 patients undergoing surgical repair. After that, we divided the population into three groups according to the time to surgery: a first group with early surgery (less than 24 h from diagnosis of the VSR) and two other groups including patients operated on day 1–3 and from day 4. A logistic regression was subsequently performed to compare each group with the early surgery group as referenced.

Results

Baseline characteristics

A total of 141 patients were included in this period, of whom 89 underwent surgical repair. The baseline characteristics of both groups (surgery and conservative) are listed in Table 1. There were no important differences between patients undergoing surgery or not except for a significant difference in age, those in the surgery group being around 10 years younger (71.1 vs. 81.6, p < < 0.001). Cardiovascular risk factors such as arterial hypertension, diabetes, obesity, or smoking were similar in both groups.

The main characteristics of the AMI episode and the VSR are summarized in Table 2. We did not observe significant differences between the surgical and medical treatment, except in the use of diagnostic coronary angiography (90.9% vs. 65.2%, p ≤ 0.001) and in surgical revascularization with coronary artery bypass grafting (CABG, 37.5% vs. 4.2%, p < 0.001). We did not find differences in the repair strategy between anterior or inferior AMI, or depending on the culprit lesion, with similar distribution of left anterior descending artery and right coronary artery in both groups. Revascularization therapy was more frequent in the surgical group.

A high number of patients had different concomitant mechanical complications, such as free wall rupture (9.4% vs. 4.4%), papillary muscle rupture (2.3% vs. 2.2%), and left ventricular pseudoaneurysm (2.4% vs. 2.2%) with no significant differences between both groups. Apical VSR was more frequent (61.6%) than basal, representing 72.1% of non-surgical cases. The median size of VSR by echocardiography was 1.5 cm (IQR 25–75: 1–2). Finally, we observed a delay between the VSR diagnosis and the AMI diagnosis of more than 24 hours in 26.7% (surgical group) to 35.2% (non-surgical) of the patients, and between symptom onset and the diagnosis of VSR in more than 24 hours in 45.7% (surgical group) to 48.8% (non-surgical) of the patients, with no differences between the groups.

Table 2. Characteristics of the myocardial infarction and ventricular septal rupture.

Variable	Surgery (n = 88)	Conservative (n = 47)	P
Anterior AMI	40 (45.5%)	27 (57.5%)	0.184
Inferior AMI	47 (53.4%)	21 (44.7%)	0.334
Coronarography	80 (90.9%)	30 (65.2%)	< 0.001
Culprit lesion:			0.407
LMCA	1 (1.3%)	0	
LAD	33 (42.3%)	13 (41.9%)	
CX	3 (3.9%)	0	
RCA	39 (50.0%)	16 (51.6%)	
Diffuse disease	1 (1.3%)	0	
No significant	1 (1.3%)	2 (6.5%)	
Dominant RCA	59 (78.7%)	22 (81.5%)	0.613
Revascularization	61 (69.3%)	23 (48.9%)	0.020
CABG	33 (37.5%)	2 (4.2%)	< 0.001
PCI	39 (44.3%)	22 (50.0%)	0.537
LVEF post-AMI	44.3; 11.0	42.7; 11.4	0.429
Mechanical complication associated:			
Free wall rupture	8 (9.4%)	1 (2.2%)	
Papillary muscle rupture	2 (2.4%)	1 (2.2%)	
Pseudoaneurysm	2 (4.4%)	0.320	
Apical VSR	53 (61.6%)	31 (72.1%)	0.240
Basal VSR	37 (43.0%)	13 (31.0%)	0.189
VSR size [cm]*	1.5 (1–2)	1.5 (1–1.7)	0.717
Patients with VSR diagnosis > 1 day after AMI diagnosis	31 (35.2%)	12 (26.7%)	0.318
Patients with VSR diagnosis > 1 day after onset of symptoms	42 (48.8%)	21 (45.7%)	0.727

*Non-normal distribution. The data are expressed as mean ± standard deviation and median [interquartile range] or number (percentage); AMI — acute myocardial infarction; CABG — coronary artery bypass grafting; LAD — left anterior descending artery; LMCA — left main coronary artery; LVEF — left ventricular ejection fraction; CX — circumflex artery; RCA — right coronary artery; VSR — ventricular septal rupture; PCI — percutaneous coronary intervention

Management and destination therapy

Table 3 summarizes the data in the management of the patients and the strategy of repair of the VSR.

The use of MCS was more frequent in the surgical group, particularly for intra-aortic balloon pump (IABP; 79.6% vs. 37.8%, p < 0.001), but also for veno-arterial extracorporeal membrane oxygenation (VA-ECMO; 18.2% vs. 6.4%, p = 0.134) and other MCS (Centrimag Levitronix, 5.7% vs. 0%, p = 0.158). There was a higher rate of vascular complications (25.9% vs. 9.8%, p = 0.036) and blood transfusions (67.5% vs. 14%, p < 0.001) in the surgical group. Renal replacement therapy was more frequent in the surgical group (29.6% vs. 12.8%, p = 0.044), as well as inotropic drugs and mechanical ventilation. These patients also had a more prolonged admission to the intensive care unit (24 vs. 3 days, p < 0.0001).

Percutaneous closure was performed in 16 patients. In 5 patients the device was implanted as a bridge to surgery and in 11 as the definitive treatment. There were low success rates for percutaneous closure, without differences between both groups (40% vs. 54.6%, p = 0.59). We observed a trend to more device migration (0% vs. 21%) in the non-surgery group. Only 1 patient treated with percutaneous closure survived (mortality of 93.8%).

Total mortality was significantly higher in the non-surgery groups, with rates of 91.5% vs. 52.3% with surgical repair (54.6% at 1 year, p < 0.001).

Hospital stay and mortality analysis of the surgical group

Tables 4 and 5 show the results related to the timing of the surgical repair, focusing on the

Table 3. In-hospital management of ventricular septal rupture.

Variable	Surgery (n = 88)	Conservative (n = 47)	P
IABP	70 (79.6%)	17 (37.8%)	< 0.001
VA-ECMO	16 (18.2%)	3 (6.4%)	0.060
Other MCS (Centrimag)	5 (5.7%)	0 (0%)	0.096
Vascular complication:	22 (25.9%)	4 (9.8%)	0.036
Bleeding	17 (20.2%)	4 (9.5%)	0.128
Transfusion	14 (16.7%)	3 (7.0%)	0.129
Vascular surgery	9 (11.7%)	0 (0%)	0.035
Transfusion needed (global)	56 (67.5%)	6 (14.0%)	< 0.001
Substitutive renal therapy	24 (29.6%)	5 (12.8%)	0.044
Inotropic drugs	71 (88.8%)	26 (66.7%)	0.004
Mechanical ventilation	69 (85.2%)	13 (34.2%)	< 0.001
Days of mechanical ventilation*	5 (2–12)	4 (3–7)	0.0001
Other definitive and bridge therapies			
Percutaneous repair	5 (5.7%)	11 (23.4%)	0.002
Successful percutaneous repair	2 (40.0%)	6 (54.6%)	0.590
PCI associated to percutaneous repair	3 (7.7%)	7 (31.8%)	0.015
Closure device migration	0 (0%)	3 (23.1%)	0.121
Prognosis and hospital stay			
ICU days (total)	24 (11–41)	3 (2–11)	0.0001
Stroke	3 (3.7%)	0 (0%)	0.249
Reinfarction	0	0	–
In-hospital mortality	46 (52.3%)	43 (91.5%)	< 0.001
One-year mortality	48 (54.6%)	43 (91.5%)	< 0.001

*Non-normal distribution. The data are expressed as mean ± standard deviation and median [interquartile range] or number (percentage); IABP — intra-aortic balloon pump; ICU — intensive care unit; MCS — mechanical circulatory support; PCI — percutaneous coronary intervention; VA-ECMO — veno-arterial extracorporeal membrane oxygenation

Table 4. Surgical management.

Variable	In-hospital mortality			1-year mortality		
	Survival (n = 43)	Death (n = 46)	Variable	Survival (n = 41)	Death (n = 48)	P
Days between VSR diagnosis and surgical repair:						
0 days (n = 29)	10 (34.4%)	19 (65.6%)		10 (34.4%)	19 (65.6%)	
1 days (n = 19)	9 (47.4%)	10 (52.6%)		9 (47.4%)	10 (52.6%)	
2 days (n = 10)	5 (50%)	5 (50%)		3 (30%)	7 (70%)	
3 days (n = 3)	1 (33.3%)	2 (66.6%)		1 (33.3%)	2 (66.6%)	
4 days (n = 4)	3 (75%)	1 (25%)		3 (75%)	1 (25%)	
5 days (n = 6)	4 (66.6%)	2 (33.3%)		4 (66.6%)	2 (33.3%)	
> 5 days (n = 24)	13 (54.1%)	11 (45.9%)	0.502	13 (54.1%)	11 (45.9%)	0.352
Days to repair	2.5 (1–6)	1 (0–5)	0.156	3.5 (1–6)	1 (0–5)	0.155
Associated CABG	9 (25.0%)	13 (30.2%)	0.605	8 (23.5%)	14 (31.1%)	0.457
MCS after surgery	13 (30.2%)	14 (31.1%)	0.929	12 (29.3%)	15 (31.9%)	0.788
Dehiscence	5 (11.6%)	13 (31.0%)	0.029	5 (12.2%)	13 (29.6%)	0.050
Surgical reintervention	6 (14.0%)	9 (21.4%)	0.366	6 (14.6%)	9 (20.5%)	0.482

CABG — coronary artery bypass grafting; MCS — mechanical circulatory support; VSR — ventricular septal rupture

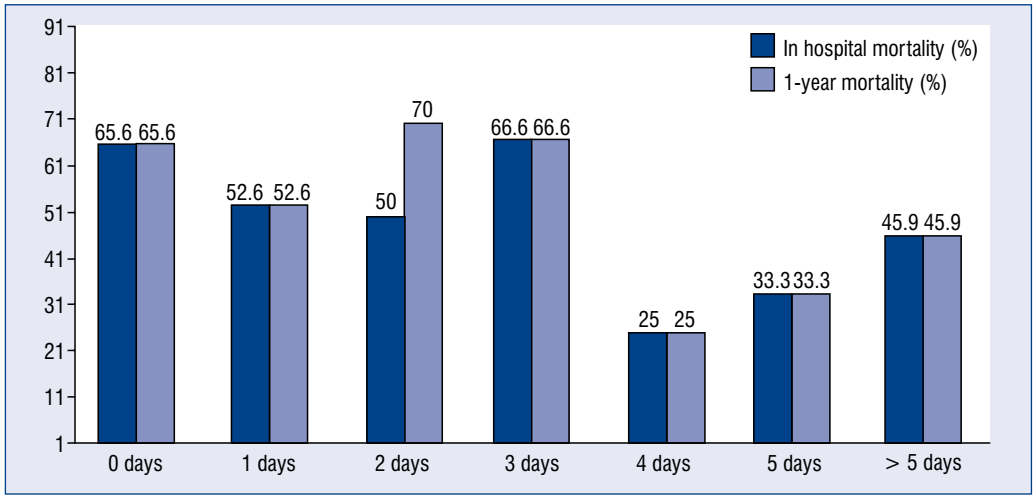

Figure 1. Surgical timing and mortality.

Table 5. Surgical timing and its relation to in-hospital mortality.

Group	Surgical timing and in-hospital mortality			
	Survivors	Death	Odds ratio	P
First 24 hours (n = 29)	10 (34.5%)	19 (65.5%)	Reference	Reference
Day 1 to 3 (n = 32)	15 (46.9%)	17 (53.1%)	0.6 (0.2–1.7)	0.327
From day 4 (n = 27)	17 (62.6%)	15 (37.4%)	0.3 (0.1–0.9)	0.036

Table 6. Multivariate analysis for total mortality in the surgical group.

Variable	Results from multivariate analysis	
	Odds ratio	P
Age (+1 year)	1.08 (1.003–1.176)	0.041
Substitutive renal therapy	4.43 (1.1–17.9)	0.036
Vascular complication	3.88 (1.02–14.64)	0.024

patients with surgical repair as a definitive treatment strategy.

We observed a trend of lower mortality (in-hospital and 1-year mortality) progressively from day zero of the VSR diagnosis, which reached its nadir on the 4th day, increasing again from this day. Figure 1 represents this low mortality window, situated from day 4, with mortality rates of 25% (day 4), 33.3% (day 5), and 45.9% (> 5 days).

In addition, we performed an analysis of mortality depending on the surgical timing (Table 5). When we compared the mortality of surgical repair in the first 24 hours after diagnosis (65.5%), as referenced, we observed that patients treated surgically from day 4 (> 96 h) had significant lower mortality rates (37.4%), with an odds ratio (OR) of 0.3 (0.1–0.9), compared with the first 24 hours. We did not observe differences in these results depending on the MCS used. The rates of dehiscence of the surgical patch in these three groups were 24%, 28.1%, and 7.7% (first 24 h, 1–3 day, from day 4, respectively; p = 0.127).

There were no significant differences in CABG use between survivors and non-survivors. Use of MCS was similar, at around 30%, in both groups. Dehiscence of VSR repair was significantly associated with a higher mortality rate (11.6% vs. 31%, p = 0.005) as well as a trend for the need for re-

operation, regardless of the cause (14% vs. 21.4%, p = 0.482). Cardiac transplant was used as rescue therapy in only 1 patient.

Prognostic factors after surgical repair

In Table 6 we present the data from the multivariate analysis of prognostic factors which increased mortality in the surgical group.

Older age (OR 1.08 per year added, 1.003–1.176, p = 0.041), the need for dialysis (OR 4.43, 1.1–17.9, p = 0.036), and the presence of vascular complications (OR 3.88, 1.02–14.64, p = 0.024) were independent markers of higher mortality in the surgical group.

Discussion

The results of this study suggest a lower mortality window for surgical repair, if performed from day 4 after VSR diagnosis. The use of MCS devices in our series varied from almost 80% for IABP to 18% for VA-ECMO, and appeared to be of utmost importance to support patients in the perioperative period, despite increasing vascular and overall bleeding complications [4, 19].

Post-AMI VSR is still a dreadful condition with high mortality rates. In our study, the 1-year mortality after surgical repair was 54.6%. Despite these high-mortality rates, surgical repair is the preferred definitive treatment for myocardial infarction-related VSR, which has to be considered, because mortality rates are higher than 90% in patients treated conservatively [4, 6, 7]. Some patients with huge defects or severe right or left ventricular dysfunction may be considered better candidates for a direct heart transplant procedure, but it is limited to specific age groups and donor availability. Percutaneous closure represents an interesting alternative for higher-risk surgical groups, or as a bail-out technique for surgical failure, but experience is limited to relatively small series [4, 8, 20]. Percutaneous closure had a disappointing mortality rate in our study (93.8%), but we have no further details on each specific procedure, and it might have been used in non-surgical candidates or in highly comorbid patients.

Current European Society of Cardiology guidelines recommended that patients who respond well to aggressive heart failure treatment and are hemodynamically stable are good candidates for an elective delayed surgical repair due to the high mortality described in the first 24 hours of surgery [20]. Previous studies suggest the optimal timing for surgery, situated usually in the first week after the diagnosis of VSR. However, these findings are based on small sample studies with variable results [12, 16, 18]. One of the strengths of this study is its multicenter design and a high sample of patients, which contributes to better clarification of the ideal time of intervention.

Allowing time for definitive scarring of VSR borders theoretically facilitates surgical repair sutures [15]. Furthermore, introducing VA-ECMO in the context of cardiogenic shock can reduce cardiac work and myocardial oxygen consumption, and improve coronary blood flow, limiting infarct extension and buying time for the hibernating myocardium to recover [21]. However, prolonged support (with MCS systems) is associated with more vascular, thrombotic, and bleeding complications [22–24]. We identified a low mortality window with significant differences in survival in patients operated following day 4 after the diagnosis of VSR. In this group the mortality was the lowest compared with the patients operated on in the first 3 days, with rates lower than 30%. After day 5, mortality increases but is still lower than the first 3 days. These data were comparable with the results of novel but smaller studies, previously mentioned, and represent an important period to plan the corrective surgery, and can facilitate the short-term use of MCS, avoiding complications related to long-term use of these therapies that can be related to differences in mortality from day 4, among other factors [25].

Mechanical circulatory support is a fundamental tool to overcome the multiorgan consequences of cardiogenic shock, which assumes a critical point in survival [11, 15, 23, 26]. These therapies can also revert a situation of multiorgan failure, being useful in the most severe patients who are faced with greater surgical mortality [27, 28]. In our study, we observed differences in the use of MCS between surgical and medical treatment in all techniques (IABP, VA-ECMO, and Centrimag™). The greater availability and experience with IABP explains the preference over other devices, such as Impella in our series [14]. The frequent use of MCS and delayed surgery can be factors related with the increase in survival shown in our previous study [14].

We also identified independent poor prognostic factors after surgery, which can complement and update others already known, such as shock situation before surgery, need for reintervention, duration of the surgery, prolonged cardiopulmonary bypass time, complex coronary lesions anatomy, or incomplete revascularization [29]. We also observed that

older age (commonly associated with poor prognosis in cardiac surgery) and the necessity of substitutive renal therapy were relevant post-operative factors that contribute to a worse prognosis. These negative predictive variables were also previously described in other series [30, 31].

We have additionally observed that patients who presented with vascular complications in the postoperative period had worse prognosis. This emergent factor is probably related with an increase in the use of MCS systems before or after surgery in hemodynamically unstable patients due to ventricular systolic dysfunction. Unfortunately, vascular access complications can lead to devastating consequences, primarily related to limb ischemia [32–34]. In these situations, it is important to develop coordinated protocols of meticulous limb examination by a qualified and multidisciplinary intensive care unit team. We observed a relatively low but significant incidence of vascular complications in our study (11.7%) compared with the data of recent reviews (around 20%) [35].

Limitations of the study

This study has some limitations that should be mentioned. The observational and retrospective character of our research, which is supported by historical data from the collaborating centers, is a potential source of selection bias. However, all selected centers have prospective databases, which helped to minimize loss of relevant information. Despite the relatively small sample size, this is one of the largest post-AMI VSR series. Inherent to its retrospective design, the decision to perform invasive or conservative treatment was based on individual evaluation rather than a prespecified protocol. For the analysis, we do not differentiate cardiogenic shock by severity grades, before the surgical repair or the use of MCS, making this relevant in the treatment of these patients. The information about the surgical repair technique was not available in our database. Finally, the contribution of only tertiary or reference centers in this database could limit extrapolation of prevalence or clinical manifestations of VSR to other settings. Despite this, we believe these details to have a limited impact in the analysis of our primary endpoint, and the present data should be taken into consideration in similar contexts.

Conclusions

Surgical repair of post-AMI VSR is still the main definitive treatment of this mechanical complication. In our study, we observed that there are differences in mortality depending on the days between the diagnosis of VSR and the surgical repair. We identified significantly lower mortality rates in patients operated from day 4 after diagnosis of VSR, compared to earlier interventions.

Older age, the necessity of substitutive renal therapy, and the presence of vascular complications were independent negative prognostic factors for the success of the surgical repair.

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Cardiac allograft vasculopathy in a long-term follow-up after heart transplantation: Role of remnant cholesterol in residual inflammation

Emyal Alyaydin[1], Christian Pogoda[1], Angelo Dell'Aquila[2], Sven Martens[2], Izabela Tuleta[1], Holger Reinecke[1], Juergen R. Sindermann[1, 2]

[1]Department of Cardiology I, Coronary and Peripheral Vascular Disease, Heart Failure, University Hospital Muenster, Muenster, Germany
[2]Department of Cardiothoracic Surgery, University Hospital Muenster, Muenster, Germany

Abstract

Background: *Cardiac allograft vasculopathy (CAV) is a major prognosis limiting factor in heart transplantation (HTx). Disease development and progression are influenced by multiple determinants, but the role of remnant cholesterol (RC) in CAV has not yet been investigated. Therefore, the present study aimed to assess the prevalence of CAV in a very long-term follow-up after orthotopic HTx and to examine the role of RC in residual inflammation despite secondary prevention.*

Methods: *Herein, is a retrospective analysis of patient data collected at the last follow-up visit in an outpatient setting. Additionally, RC levels were calculated based upon cholesterol profile.*

Results: *The study population consisted of 184 patients with a mean follow-up of 15.0 ± 6.8 years. More than 40% of the overall cohort had CAV at last follow-up. The mean RC was 27.1 ± 14.7 mg/dL. Patients with CAV had significantly elevated RC despite intensified statin treatment ($p = 0.018$). A positive correlation was observed between RC and interleukin-6 as a marker of residual inflammation. Elevated RC and prolonged follow-up emerged as significant factors related to CAV in a multivariate analysis (odds ratio [OR] 2.9, 95% confidence interval [CI] 1.5–5.5, $p = 0.001$ and OR 3.3, 95% CI 1.4–7.7, $p = 0.006$, respectively), whereas mycophenolate mofetil was inversely associated with CAV (OR 0.4, 95% CI 0.2–0.9, $p = 0.034$).*

Conclusions: *Remnant cholesterol has proinflammatory properties and is associated with CAV development in HTx. Thus, RC should be concerned as an additional tool for risk assessment.* (Cardiol J 2022; 29, 5: 782–790)

Key words: cardiac allograft vasculopathy, remnant cholesterol, statin treatment, heart transplantation

Introduction

Cardiac allograft vasculopathy (CAV) is a relevant prognosis limiting condition in patients who have undergone heart transplantation (HTx) [1]. It is characterized by a diffuse involvement of the graft's coronary circulation, thus limiting the success of interventional treatment attempts. Research to elucidate the potential risk factors accelerating the CAV development has revealed that beyond the classic cardiovascular risk factors, immunological determinants and inflammation also

Address for correspondence: Emyal Alyaydin, MD, PhD, Department of Cardiology I, Coronary and Peripheral Vascular Disease, Heart Failure, University Hospital Muenster, Albert Schweitzer Campus 1, 48149 Muenster, Germany, tel: +49 152 042 509 62, e-mail: e.alyaydin@gmx.de

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contribute to disease progression [1–4]. Therefore, statin therapy is routinely recommended in all HTx patients, as it has been shown to have pleiotropic effects, to reduce CAV and to improve long-term outcomes regardless of lipid levels [5]. Nevertheless, recent data have revealed that remnant cholesterol (RC), composed of very low-density and intermediate-density lipoproteins in the fasting state, and additionally chylomicron remnants in the non-fasting state, is a relevant cardiovascular risk factor with proinflammatory properties. However, results regarding the efficacy of statin treatment in reducing RC levels remain inconsistent, and the effect of RC on CAV after HTx has not yet been assessed [6, 7].

Methods

Study design

This is a retrospective analysis of data collected at the most recent follow-up visit in the documented outpatient clinic for terminal heart failure and HTx. The patient population consisted of 268 cardiac transplant recipients, who were monitored and/or underwent HTx at this same institution. The time span between the first HTx and the last follow-up was 33 years (December 29th, 1987 – July 29th, 2021). Unfortunately, 80 patients were excluded because of insufficient data or clinical infection. In addition, 4 patients were not included as heart-lung-transplantation, retransplantation, and short-term follow-up (< 1 year) were considered exclusion criteria (Fig. 1).

The routine patient monitoring after HTx was based on on-site examinations in 3-month intervals. Available data on patient history, current complaints and dynamic of subjective symptoms, clinical and laboratory investigations were collected at every visit, whereas transthoracic echocardiograms were obtained every 6 months. The conducted results were thoroughly interpreted by experienced cardiologists. Based on the findings, additional tests were carried out if needed.

Laboratory parameters

The laboratory assessment consisted of complete blood count including lymphocyte subpopulations, lipid profile, coagulation results, basic liver and renal function panels, inflammatory parameters, N-terminal prohormone of B-type natriuretic peptide (NT-proBNP) and serological examination to exclude subclinical infections. All measurements were performed in a fasting state. Additionally, RC levels were calculated using the formula:

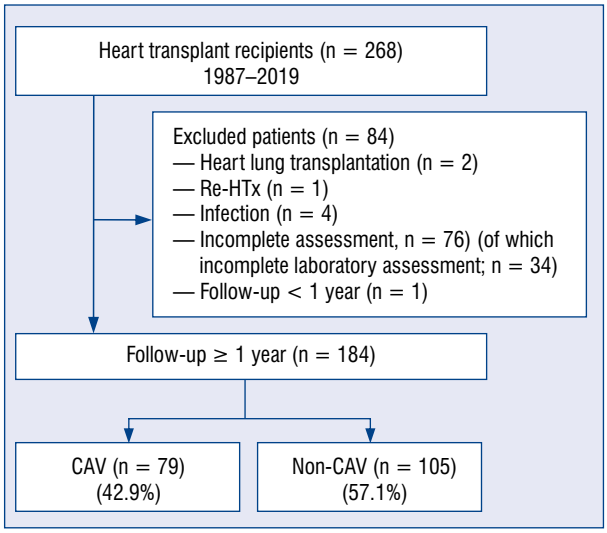

Figure 1. Flowchart of the study; HTx — heart transplantation; CAV — cardiac allograft vasculopathy.

RC = total cholesterol – low density lipoproteins cholesterol (LDL-C) – high density lipoproteins cholesterol (HDL-C). LDL-C was directly measured. Although the study population was treated with different statins in variable doses, most patients were on pravastatin. Therefore, to exclude possible bias related to statin dose, pravastatin equivalent dose (PED) was calculated.

Definition of CAV

Cardiac allograft vasculopathy was defined in accordance with the nomenclature of the International Society for Heart and Lung Transplantation. This classification is based on invasive coronary angiography (ICA) results in combination with an assessment of the cardiac allograft function. The recommendation to use primarily ICA is due to its universal availability and potential to provide the highest level of evidence. In contrast, the ability of intravascular ultrasound to deliver any additional diagnostic or therapeutic aid in CAV is considered limited, and optical coherence tomography is has not yet been incorporated in the diagnostic algorithm [1]. Therefore, the stratification of patients into two groups was performed according to whether CAV was present on any ICA in the time course after HTx: non-CAV (corresponding ISHLT CAV_0) and CAV group (≥ ISHLT CAV_1). Thus, the non-CAV group was comprised of patients without detectable angiographic lesions, and the CAV cohort encompassed subjects with any angiographically detectable stenoses, irrespective of the graft function (CAV_1, CAV_2, and CAV_3).

The study was performed in compliance with the Declaration of Helsinki and data sampling was approved by the local ethics committee (2019-021-f-S).

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics software, version 27. Mean ± ± standard deviation was used to describe continuous variables and numbers (percentage) for categorical variables. Comparative assessment of parametric values was performed with Student t test and categorical variables with the χ^2 test. Two-tailed bivariate interactions were assessed with the Pearson correlation coefficient. The potential influence of risk factors was examined with the univariable proportional hazards model, and variables with $p < 0.1$ were introduced in a multivariable regression analysis with backward selection after assessment for collinearity. For all conducted analyses $p < 0.05$ was defined as statistically significant.

Results

Baseline characteristics

The study population consisted of 184 HTx recipients with a mean follow-up of 15.0 ± 6.8 years. More than 40% of the overall study population had CAV and the prevalence among survivors was almost 50% at 10-year follow-up (Fig. 2). No relevant differences were observed in the underlying etiology of terminal heart failure prior HTx between groups (Table 1). In particular, the ischemic nature of the antecedent disease was not more prevalent in the CAV population. Moreover, no relevant differences in past rejection episodes or rejections requiring therapy were found between the CAV and non-CAV groups (Table 1). Notably, the classic cardiovascular risk factors, except diabetes, had comparable prevalence in the two groups. Although the left ventricular ejection fraction (LVEF) was in the normal range in the population, patients with CAV had slightly more impaired LVEF, significantly elevated NT-proBNP, and a poorer functional class according to the New York Heart Association (NYHA) classification [8]. Additionally, cerebral/peripheral vascular disease (CAD/PAD) were more common in the CAV group (Table 1).

Medical treatment

Approximately 50% of the patients were on a cyclosporin A based immunosuppressive regime without significant differences between either group. Everolimus was more common in patients with CAV, whereas mycophenolate mofetil (MMF)

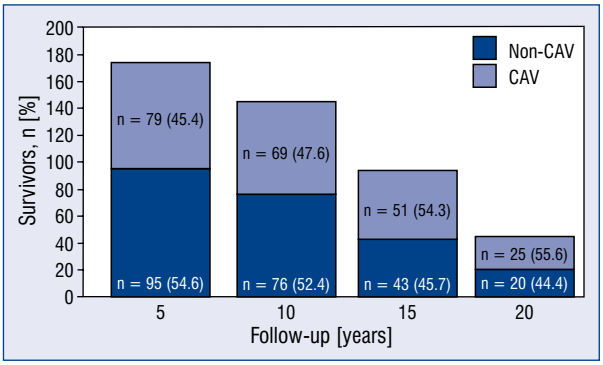

Figure 2. Prevalence of cardiac allograft vasculopathy (CAV) in survivors. Data are presented as number (percentage).

was commonly used as a concomitant immunosuppressant in the non-CAV cohort. Comparative assessment of the medication revealed no relevant differences in the frequency of use of beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. As a calcineurin sparing agent, diltiazem was a regular medication among one-third of the study population. Patients with CAV were more often on diuretics. More than 80% of the patients in both groups were taking statins with a higher intensity of the therapy in the CAV group. Ezetimibe was more commonly prescribed in the CAV group (Table 2).

Lipid profile and inflammation

Since most of the patients were on statin treatment, there was no significant contrast between the LDL-C levels among both study groups. As depicted in Figure 3A–C, no differences were observed in the triglyceride (TGL) or HDL levels, except for in the RC values between the study groups. The mean calculated RC was 27.1 ± 14.7 mg/dL and was markedly higher in CAV. The assessment of the dose response to statin treatment, revealed a significant negative correlation of PED with the LDL-C levels ($p < 0.001$) but not with the absolute RC measures ($p = 0.818$) or with RC values exceeding 27 mg/dL ($p = 0.370$). Ezetimibe also had no influence on the RC levels in the same setting ($p = 0.934$ and $p = 0.505$, respectively). Moreover, the statin choice was not associated with the estimated RC levels ($p = 0.489$, when treated with atorvastatin, $p = 0.934$ with fluvastatin, $p = 0.157$ with pravastatin, $p = 0.657$ with rosuvastatin, and $p = 0.987$ with simvastatin). Notably, CAV had no influence on the statin preferences, but patients with CAV were on a more intensive statin treatment and is expressed as PED (Table 2).

Table 1. Characteristics of the patients at last follow-up.

Patient characteristics	Non-CAV	CAV	P
Demographics			
Age at HTx [years]	43.5 ± 16.7	46.4 ± 13.5	0.191
Follow-up [years]	13.6 ± 7.1	16.9 ± 5.9	0.001*
Male	84 (80.0%)	63 (79.9%)	1.000
Survivors	80 (76.2%)	56 (70.9%)	0.498
Antecedent disease			0.195
Ischemic cardiomyopathy	37 (35.2%)	29 (36.7%)	
Dilated cardiomyopathy	43 (41.0%)	41 (51.9%)	
Others	25 (23.8%)	9 (11.4%)	
Rejections			
Rejection episodes	59 (56.2%)	43 (54.4%)	0.881
Rejections requiring therapy	38 (36.2%)	30 (38.0%)	0.878
Clinical and laboratory examination			
Body mass index [kg/m^2]	26.0 ± 5.5	26.2 ± 5.4	0.776
Heart rate [bpm]	95.4 ± 90.0	82.0 ± 13.3	0.192
Systolic BP [mmHg]	126.0 ± 18.0	124.5 ± 18.9	0.588
Diastolic BP [mmHg]	79.4 ± 10.7	79.0 ± 10.9	0.824
NYHA class > 1	73 (69.5%)	66 (83.5%)	0.037*
NT-proBNP	3511.6 ± 6711.8	6104.7 ± 9033.1	0.034*
eGFR [mL/min/1.73 m^2]	49.3 ± 27.4	40.3 ± 23.2	0.109
Echocardiographic assessment			
LVEF [%]	58.4 ± 5.8	55.1 ± 9.2	0.006*
TAPSE [mm]	16.2 ± 3.6	16.4 ± 5.0	0.843
Comorbidities			
Arterial hypertension	83 (79.0%)	63 (79.7%)	1.000
Diabetes	26 (24.8%)	31 (39.2%)	0.038*
Dyslipidemia	89 (84.8%)	72 (91.1%)	0.261
End-stage-renal-disease	21 (20.0%)	14 (17.7%)	0.850
Precarcinoma/malinancy	29 (27.6%)	27 (34.2%)	0.419
Restrictive/obstructive lung disease	17 (16.2%)	15 (19.0%)	0.696
CAD/PAD	9 (8.6%)	17 (21.5%)	0.018*
Cytomegalovirus	15 (45.5%)	18 (54.5%)	0.174

Data are presented as mean ± standard deviation or number (percentage). HTx — heart transplantation; CAV — cardiac allograft vasculopathy; BP — blood pressure; NYHA class — functional assessment according to the New York Heart Association classification; NT-proBNP — N-terminal-pro hormone B-type natriuretic peptide; eGFR — estimated glomerular filtration rate; LVEF — left ventricular ejection fraction; TAPSE — tricuspid annular plane systolic excursion; CAD/PAD — cerebral/peripheral vascular disease; *p < 0.05

Furthermore, no differences were observed in routinely estimated levels of C-reactive protein (CRP) between both study groups, whereas interleukin-6 (IL-6) was significantly increased (Fig. 3A–C). Elevated RC (≥ 27 mg/dL) was associated with increased levels of IL-6 (IL-6 > 10 mg/dL, p = = 0.025). An RC level ≥ 27 mg/dL was identified as a significant factor associated with CAV in univariate and multivariate analyzes (Fig. 4).

Remnant cholesterol and CAV

Remnant cholesterol ≥ 27 mg/dL was also associated with CAV in a multivariate logistic regression analysis after adjustment for TGL, LDL-C, statin treatment and immunosuppressive regimes (odds ratio [OR] 2.6, 95% confidence interval [CI] 1.4–4.9, p = 0.003). As only a limited number of patients were treated with azathioprine (n = 6, 3.3% and there was only 1 subject without CAV),

Table 2. Medication.

	Non-CAV	CAV	P
Cardiovascular medication			
Beta-blockers	55 (52.4%)	52 (65.8%)	0.072
Calcium chanel blockers	28 (26.7%)	18 (22.8%)	0.608
Diltiazem	31 (29.5%)	22 (27.8%)	0.870
ACEI/AT II receptor antagonists	58 (55.2%)	47 (59.5%)	0.652
Diuretics except aldosterone antagonists	56 (53.3%)	59 (74.7%)	0.003*
Aldosterone antagonists	9 (8.6%)	15 (19.0%)	0.047*
Statins:	88 (83.8%)	64 (82.1%)	0.843
Atorvastatin	25 (23.8%)	29 (36.7%)	0.072
Fluvastatin	2 (1.9%)	2 (2.5%)	1.000
Pravastatin	49 (46.7%)	27 (34.2%)	0.098
Rosuvastatin	1 (1.0%)	1 (1.3%)	1.000
Simvastatin	10 (9.5%)	8 (10.1%)	1.000
Pravastatin equivalent dose [mg/d]	43.0 ± 52.1	62.0 ± 57.1	0.021*
Ezetimibe	6 (5.7%)	17 (21.5%)	0.003*
Platelet aggregation inhibitors	27 (25.7%)	62 (78.5%)	< 0.001*
Oral anticoagulants	14 (13.3%)	18 (22.8%)	0.116
Immunosuppressants medication			
Immunosuppressant:			
Cyclosporin A	58 (55.2%)	40 (50.6%)	0.554
Mycophenolate mofetil	91 (86.7%)	57 (72.2%)	0.016*
Everolimus	29 (27.6%)	36 (45.6%)	0.013*
Tacrolimus	26 (24.8%)	16 (20.3%)	0.485
Azathioprine	1 (1.0%)	5 (6.3%)	0.086
Prednisone	74 (70.5%)	55 (69.6%)	1.000

Data are presented as number (percentage). CAV — cardiac allograft vasculopathy; ACEI — angiotensin-converting enzyme inhibitors; AT II — angiotensin II; *p < 0.05

azathioprine was excluded from the analysis. The estimated r^2 in a linear regression analysis using the same model was 0.121 (p = 0.002).

The positive predictive value (PPV) of RC ≥ 27 mg/dL for CAV was 60.8% (p = 0.001), whereas no correlation for the TGL values exceeding 150 mg/dL was observed (PPV 48.1%, p = 0.174).

Additional factors

In addition to RC, IL-6, diabetes, and CAD/PAD emerged as associated with CAV in HTx. As expected, the disease prevalence was significantly higher in a prolonged follow-up. An assessment of the potential association of the immunosuppressive medication with CAV in a univariate analysis revealed a positive correlation with everolimus and an inverse association with MMF (Fig. 4A). However, the results regarding the immunosuppressive regime should be interpreted with caution, as most patients were treated with cyclosporin A, MMF, and prednisone in the first years after HTx, and the medication was changed in some cases in the time course of 15 years. Additionally, everolimus was recently the immunosuppressant of choice in the CAV group.

In a multivariate analysis RC, prolonged follow-up and MMF-based immunosuppression were the factors significantly associated with CAV development after adjustment for the remaining covariates (Fig. 4B).

Discussion

Under investigation was the association of RC with residual inflammation in patients with CAV in a very long-term follow-up after HTx. Additionally, the potential influence of secondary prevention through statin use on its serum levels was to be elucidated. According to available research, this is the first study to examine the role of the lipid remnants for the ischemic distress of transplanted hearts.

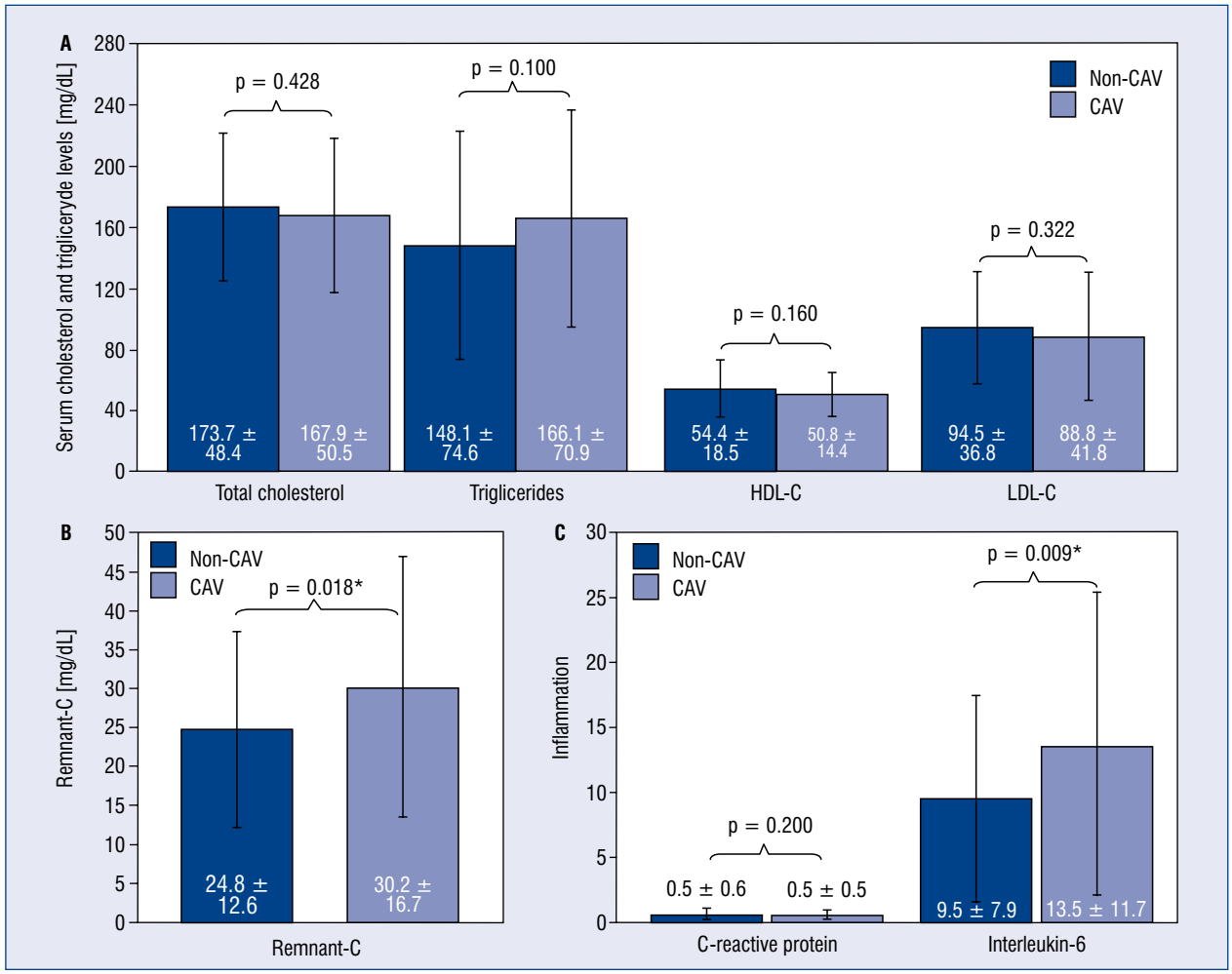

Figure 3. Serum cholesterol (**A**), remnant cholesterol (**B**) and inflammatory (**C**) parameters in cardiac allograft vasculopathy (CAV). Data are presented as mean ± standard deviation; Remnant-C — remnant cholesterol, HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol.

Disease prevalence

The burden of CAV among the survivors was increasing over the years after HTx, with a prevalence of 45.4%, 47.6%, 54.3% and 55.6% at 5, 10, 15 and 20 years, respectively (Fig. 2). Thus, the disease prevalence was higher at 5-year follow-up as previously reported, whereas the results at 10-year follow-up were consistent with available data [5]. A potential explanation for the present observations may be the difference in the diagnostic algorithms in follow-up. In accordance with the guidelines for adult HTx recipients, annual or biannual coronary angiographies were performed in the first years after HTx. If patients were free of CAV, less frequent invasive assessment was considered [5]. Thus, the results in long-term follow-up were often acquired during coronary angiographies conducted because of an acute coronary syndrome, cardiac decompensation, prior non-invasive assessment indicating ischemia, or clinical/laboratory results suggesting rejections. Additionally, CAV was diagnosed with ICA, which might have led to an underestimation in comparison to intravascular ultrasound or optical coherence tomography.

Underlying etiology

In assessing the influence of classic cardiovascular risk factors, both study groups were homogenous, except that diabetes and CAD/PAD were significantly more prevalent in CAV.

Previous research findings into the role of diabetes in CAV have been contradictory; whereas some studies have suggested that diabetes is not relevant, others have reported that it significantly influences CAV development and progression [9, 10]. In the current population, diabetics had

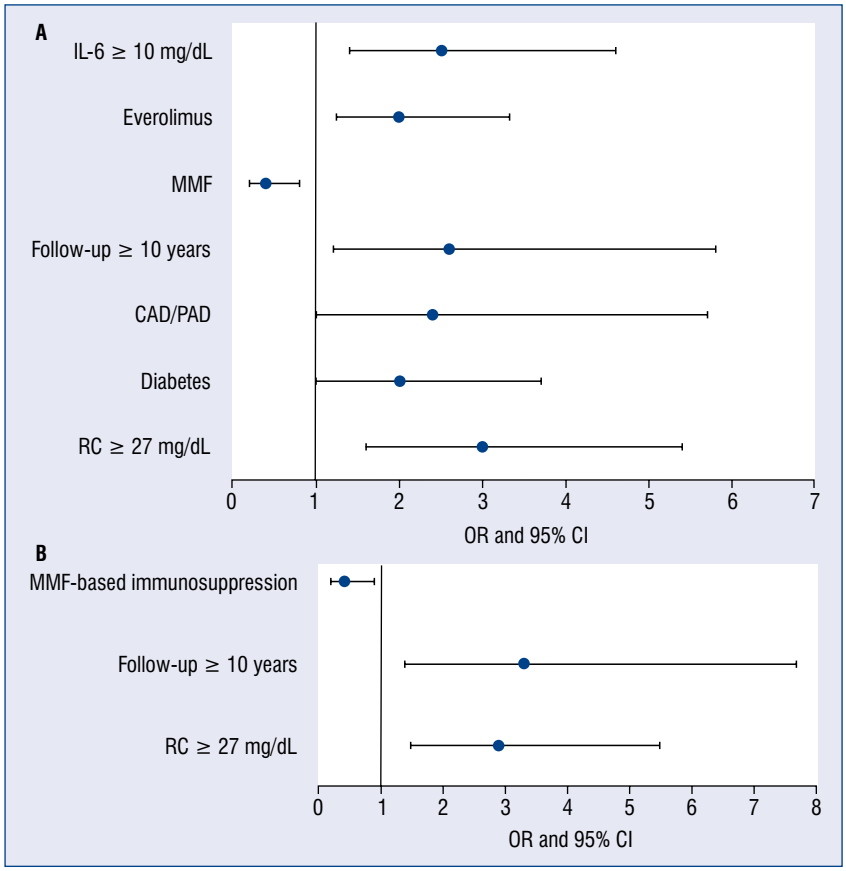

Figure 4. Factors associated with cardiac allograft vasculopathy; **A.** Univariate logistic regression analysis; **B.** Multivariate logistic regression analysis with stepwise backward selection; RC — remnant cholesterol; CAD/PAD — cerebral/peripheral vascular disease; MMF — mycophenolate mofetil; IL-6 — interleukin 6; OR — odds ratio; CI — confidence interval.

additionally elevated RC levels (RC ≥ 27 mg/dL, p = 0.026) and IL-6 (p = 0.023), revealing the possible interactions between metabolic factors and inflammation.

In addition, in line with previous findings, CAD and PAD were relevant concomitant diseases in CAV [11]. No routine sonographic screening was performed in the current patient population, resulting in a potential underestimation of disease prevalence. Ischemic cardiomyopathy before HTx was a significant predictor of CAD/PAD (OR 5.0, 95% CI 2.0–12.3, p < 0.001), and these patients more often had diabetes (p = 0.037). Thus, pretransplant predisposition to vascular disease may have consequences in posttransplant care, although no direct correlation between antecedent ischemic cardiomyopathy and CAV was observed.

Clinical consequences

As expected, patients with CAV had a more impaired left ventricular systolic function, thus resulting in significantly elevated NT-proBNP levels and consecutive functional impairment, expressed as NYHA functional class. In addition, CAV was associated with slightly more impaired renal function, although the difference was not statistically significant. The prevalence of end-stage renal disease was also comparable. Consequently, no relevant correlation was observed between the estimated glomerular filtration rate and NT-proBNP values. Therefore, the confounding effect of renal function on NT-proBNP and on patient functional status is limited and primarily CAV appears to cause the observed functional impairment.

Statins as a "panacea"

Most of the patients were on statin treatment, but only 28.8% of the overall study population attained the LDL-C target levels recommended by the 2016 European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines for the management of dyslipidemias [12]. However, taking potential interactions with the immunosuppressants into consideration, the guidelines for

the care of heart transplant recipients recommend lower statin doses [5]. Furthermore, recent studies had reported a protective effect against CAV when a median LDL concentration of < 100 mg/dL was attained and no further benefit of a target concentration of < 70 mg/dL [13]. Additionally, as patients with CAV were on an intensified statin treatment, there were no significant differences between both study groups ($p = 0.189$), thus minimizing potential bias related to LDL-C values.

In contrast to findings from previous studies, there were no significant differences in CRP values between both patient groups and no relevant influence of statin treatment on its plasma levels was observed [14]. This finding may be attributable to retrospective character of the present study and the more intensive disease-modifying therapy in CAV. Herein, patients were clinically free of manifest infections. Thus, the estimated CRP levels were in the normal range or only slightly increased due to expected fluctuations. However, the IL-6 levels were remaining significantly elevated, thus indicating residual inflammation.

Kindling inflammation in CAV

Elevated IL-6 values (IL-6 ≥ 10 mg/dL) correlated with increased serum RC (RC ≥ 27 mg/dL, $p = 0.025$). This result is in line with previous findings reporting relevant inflammatory potential of RC and its role in atherosclerosis [6, 15]. Studies to date have shown that IL-6 is the strongest predictor of mortality among inflammatory parameters indicating that the future management of atherosclerosis may require inhibition of inflammation in addition to cholesterol-lowering. Additionally, IL-6 and CRP may continue to predict high cardiovascular risk, despite aggressive contemporary care including statin therapy, angiotensin inhibitors, beta-blockers, antithrombotic therapy, and high rates of coronary revascularization [16]. The limited predictive value of CRP in the present study may also be a consequence of the use of standard CRP measurements rather than high sensitivity CRP, thus potentially resulting in "mild" inflammation not being detected.

Additional factors

In a univariate analysis, everolimus and MMF-based immunosuppressive regimes emerged to be associated with CAV. Everolimus was previously reported to influence CAV development, and subsequent attempts to treat de novo coronary stenoses with everolimus-eluting stents which have shown promising results in short- and long-term follow-up [17–19]. In addition, MMF may also improve survival and be beneficial in CAV [20]. However, in our population, the benefits of the mentioned drugs, exceeding their immunosuppressive characteristics, were confirmed only for MMF. This finding might be explained by the retrospective nature of the study and the fact that most of the patients were on a cyclosporin A/MMF-based regimen for years and were lacking to experience the potential beneficial effect of the proliferation inhibitors due to short term follow-up. Additionally, given its protective effects, everolimus was recently the remedy of choice in CAV, thus limiting the predictive value of the immunosuppressive regime in an observational setting.

Future perspectives and treatment alternatives

When it comes to therapeutic alternatives against cholesterol remnants, PCSK9-inhibitors are known to reduce LDL-C levels and influence RC levels [21]. Unfortunately, none of the current patients were treated with PCSK-inhibitors, so evidence cannot be shown on their effectiveness. However, evidence in heart transplant recipients and data regarding their potential influence on CAV is still limited, and further results are expected to be announced in the coming years [22, 23].

Limitations and strength of the study

The major limitation of this study is its monocentric design, which limited the number of patients enrolled. However, the scarcity of donors and the volume of HTx should also be taken into consideration. The present study was based on a complete assessment in the relatively large cohort of 184 orthotopic heart transplant recipients and can deliver a solid base for further research to advance transplant care.

Additionally, the immunosuppressive regime was subject to change over the time course of 15 years after HTx according to the patients' clinical condition and commodities, limiting the predictive value of the data regarding the influence of the immunosuppressants in an observational setting. Therefore, these results should be interpreted with caution.

Conclusions

Cardiac allograft vasculopathy is a socially significant disease in HTx causing relevant functional impairment with increasing age. RC may effectively overcome the scope of the statins and promote inflammation in the coronary circulation of allografts, despite being largely overlooked in comparison to the far more prominent blood cho-

lesterol carriers. The estimation of RC requires no extra cost but can aid in residual risk assessment. Additionally, MMF had protective effects against CAV in long-term follow-up.

Conflict of interest: None declared

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Leveraging clinical decision support tools to improve guideline-directed medical therapy in patients with atherosclerotic cardiovascular disease at hospital discharge

Anish Vani[1, 2], Karen Kan[1, 2], Eduardo Iturrate[1], Dina Levy-Lambert[1], Nathaniel R. Smilowitz[1, 2], Archana Saxena[1, 2], Martha J. Radford[1, 2], Eugenia Gianos[3]

[1]Department of Medicine, NYU Langone Health, New York, United States
[2]Division of Cardiology, NYU Langone Health, New York, United States
[3]Department of Cardiology, Lenox Hill Hospital, Northwell Health, New York, United States

Abstract

Background: *Guidelines recommend moderate to high-intensity statins and antithrombotic agents in patients with atherosclerotic cardiovascular disease (ASCVD). However, guideline-directed medical therapy (GDMT) remains suboptimal.*

Methods: *In this quality initiative, best practice alerts (BPA) in the electronic health record (EHR) were utilized to alert providers to prescribe to GDMT upon hospital discharge in ASCVD patients. Rates of GDMT were compared for 5 months pre- and post-BPA implementation. Multivariable regression was used to identify predictors of GDMT.*

Results: *In 5985 pre- and 5568 post-BPA patients, the average age was 69.1 ± 12.8 years and 58.5% were male. There was a 4.0% increase in statin use from 67.3% to 71.3% and a 3.1% increase in antithrombotic use from 75.3% to 78.4% in the post-BPA cohort.*

Conclusions: *This simple EHR-based initiative was associated with a modest increase in ASCVD patients being discharged on GDMT. Leveraging clinical decision support tools provides an opportunity to influence provider behavior and improve care for ASCVD patients, and warrants further investigation.* (Cardiol J 2022;, 29, 5: 791–797)

Key words: cardiovascular disease, secondary prevention, guideline-directed medical therapy, optimal medical therapy, best practice alerts, clinical decision support tools, electronic health records

Introduction

Secondary prevention guidelines from major medical societies in the United States emphasize at least moderate to high-intensity statins, antiplatelet agents, and lifestyle change in patients with established atherosclerotic cardiovascular disease (ASCVD) (AHA/ACC, AACE, NLA, IAS) [1–5] based on an abundance of data demonstrating both morbidity and mortality benefit [6, 7]. However, patient medical regimens and risk factors remain suboptimal in clinical practice [8–10], and even in large randomized controlled trials where emphasis is placed on optimal medical therapy [11]. Inpatient interventions to improve utilization and adherence to secondary prevention strategies may improve outcomes. At our own institution, we previously reported improvements in guideline-

Address for correspondence: Eugenia Gianos, MD, Associate Professor of Medicine, System Director, Cardiovascular Prevention, Northwell Health, Director, Women's Heart Health, Lenox Hill Hospital, 110 East 59th Street - Suite 8A, New York, NY 10020, USA, tel: 212-434-6160, fax: 212-434-6971, e-mail: EGianos@northwell.edu

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directed medication therapy (GDMT) associated with inpatient preventive cardiology consultations, and a prescription given at the time of discharge was associated with improved medicine regimens at 6-month follow-up [12]. In addition, lifestyle education at the time of discharge is not universal [13]. Patients may leave the hospital without understanding the potential benefit of lifestyle changes, which risk factors need to be improved, and how best to optimize their cardiovascular risk.

Clinical decision support instruments built into electronic health record (EHR) systems provide an opportunity to improve provider adherence to cardiovascular clinical practice guidelines. These instruments have been shown to increase the appropriateness of antimicrobial prescribing in the inpatient setting [14, 15]. Customized educational hand-outs specific to patient diagnosis at the time of discharge printed in the EHR after-visit summary can ensure that all patients receive the same basic information and resources for lifestyle improvement. Educational materials are currently available online from many organizations (Cardiosmart, National Lipid Association, American Heart Association) and can be customized based on institutional guidelines.

The impact of clinical decision support and educational materials provided in the after-visit summary on utilization and adherence to cardiovascular secondary prevention guidelines has not been established. We sought to determine the impact of a quality improvement initiative using clinical decision support to optimize adherence to GDMT and patient education at the time of hospital discharge in patients with established ASCVD.

Methods

Patients

Adults age ≥ 18 years with an established diagnosis of ASCVD discharged from inpatient hospitalization, medical observation, or ambulatory procedures at New York University Langone Health from February 2016 to February 2018 were eligible for inclusion. A diagnosis of ASCVD was defined by ≥ 1 ASCVD-associated diagnoses in the principal problem list of the EHR. Patients were excluded if they expired during the hospitalization, were discharged to hospice, had a known allergy to statin therapy, or had liver enzymes that were greater than two-times the upper limit of normal. Among patients with multiple visits during the study timeframe, only the first eligible encounter was included in the primary analysis.

Clinical decision support interventions

As part of ongoing quality improvement initiatives at New York University Langone Health, the Division of Value Based Medicine championed a 'discharge-centered' secondary prevention program to improve compliance with the medical center's Clinical Practice Guidelines for patients with ASCVD. In collaboration with our institution's Medical Center Information Technology group, we developed best practice alerts (BPAs) in the EHR to serve as real-time reminders about GDMT to providers caring for inpatients with ASCVD. The first BPA was designed as a 'passive' notification of recent hemoglobin A1c (HbA1c) and lipid results that included an optional one-click order to repeat lipid and HbA1c laboratory testing. The second and third BPAs were designed to interrupt the provider's workflow with recommendations for statin and antithrombotic therapy at the time of discharge and included a link to prescribe appropriate statin and/or antithrombotic therapy. These alerts were targeted to selected patients with an ASCVD diagnosis who did not have an existing prescription for moderate or high-intensity statin or antithrombotic therapy. The BPAs allowed providers to decline statin and antithrombotic therapy orders and provide a rationale for this clinical decision. The BPA for statin therapy at discharge was not displayed for patients with documented statin allergies in the EHR.

Patient education intervention

To complement the decision support intervention, patient educational materials were developed for patients with ASCVD. These materials provided descriptions of ASCVD diagnoses, optimal diets for risk reduction, physical activity recommendations, and patient lifestyle resources. To allow patients to understand their own ASCVD risk factor control, each form was customized with patient-specific values for HbA1c, blood pressure, low-density lipoprotein cholesterol (LDL-C), body mass index (BMI), smoking status, and the corresponding target values. Patient educational materials were distributed via the EHR-generated after-visit summary provided at discharge to all eligible patients with ASCVD.

Provider education

Once the BPAs and educational material in the after-visit summary were fully incorporated into the EHR, hospital providers (nurse practitioners, physician assistants, and graduate medical education trainees) were notified about the initiative and

Table 1. Baseline characteristics in the pre- and post-best practice alert implementation cohorts.

	Total cohort (n = 11,553)	Pre-implementation (n = 5985)	Post-implementation (n = 5568)	P
Age [years]	69.1 ± 12.8	69.2 ± 12.8	68.9 ± 12.8	0.27
Male sex	58.5%	57.7%	59.3%	0.07
Admission statin	66.2%	64.8%	67.7%	0.001
Admission antithrombotic	74.3%	73.8%	74.9%	0.18

provided hospital ASCVD guidelines. Representatives of each hospital inpatient, observation, and ambulatory unit received dedicated education from a member of the Division of Cardiology during the initial implementation phase.

Assessment of the quality improvement intervention and outcomes

The EHR-based intervention was launched on July 24, 2017, and the education of providers was conducted between June and September 2017. In order to evaluate the impact of the EHR-based intervention, data was collected over two 5-month periods, prior to (January 2017 to May 2017), and following (October 2017 to February 2018), the full implementation of the EHR-based intervention. The primary outcome of interest was the proportion of ASCVD patients prescribed GDMT with a moderate or high-intensity statin and antithrombotic therapy at the time of discharge. Data regarding actions in response to the interruptive BPAs was collected to understand provider behavior. Additional data collected from the electronic medical record included patient demographics, HbA1c, total cholesterol, LDL, serum liver enzymes, hospital service, and discharge diagnosis. Preadmission and discharge medication lists were obtained from the EHR. Moderate and high-intensity statins were classified based on ACC/AHA definitions. Specifically, high-intensity statins included atorvastatin 40 mg, atorvastatin 80 mg, rosuvastatin 20 mg, and rosuvastatin 40 mg. Moderate-intensity statins included atorvastatin 10 mg, atorvastatin 20 mg, rosuvastatin 5 mg, rosuvastatin 10 mg, pravastatin 40 mg, simvastatin 40 mg, and lovastatin 40 mg. Eligible antithrombotic therapy included acetylsalicylic acid, clopidogrel, prasugrel, ticagrelor, vorapaxar, as well as warfarin, rivoraxaban, dabigatran, apixiban, and edoxaban.

Statistical analysis

Continuous variables were reported as means and standard deviations and were compared by the Student t-test. Categorical variables were reported as proportions and compared by χ^2 tests. Univariate and multivariable regression was performed to identify predictors of discharge on GDMT after adjusting for age, sex, admission type, admitting service, and whether the admission occurred before or after implementation of the BPA and patient education intervention. Statistical significance was defined as two-tailed $p < 0.05$ for all tests. Statistical analysis was performed using the R Foundation for Statistical Computing's R version 3.5.0 (Vienna, Austria).

Results

Among 11,553 patients who were included in the analysis, the mean age was 69.1 ± 12.8 years, 58.5% were male, and 66.2% and 74.3% were on a statin and antithrombotic agent on admission, respectively (Table 1). The pre-BPA (n = 5985) and post-BPA (n = 5568) cohorts were similar with regards to baseline characteristics; however, a greater proportion of patients in the post-BPA cohort were on a statin on admission (67.7% vs. 64.8%, p = 0.001). Patients were primarily treated on a cardiology (37.9%), medicine (27.6%), or surgical (20.2%) service. A majority of patients were treated in the outpatient setting for an ambulatory procedure (57.6%) or the inpatient setting (32.8%).

Comparing pre- and post-BPA implementation, there was a 4.0% increase in discharge statins, 3.6% increase in high-intensity statins, and 3.1% increase in antithrombotic agents in the post-BPA cohort ($p < 0.001$ for all comparisons) (Fig. 1). There were significant increases in the rates of statin prescriptions at discharge among inpatients, patients undergoing ambulatory procedures, and among patients admitted to a medicine or surgical service (Fig. 2A, B). A significant increase in discharge antithrombotic rates among surgical patients was also observed (Fig. 2C, D). There were 5.3% and 6.8% new antithrombotic prescriptions at discharge compared to admission in the pre- and

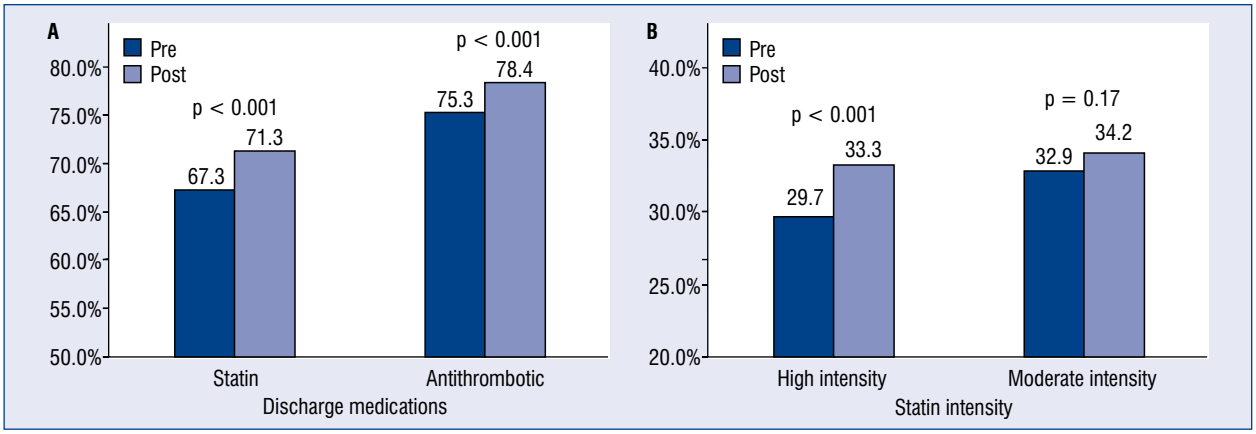

Figure 1. Rates of guideline-directed medical therapy on hospital discharge; **A.** Compares pre- and post-best practice alert implementation rates of discharge statin and antithrombotic rates; **B.** Compares the breakdown of moderate and high-intensity statin rates on discharge.

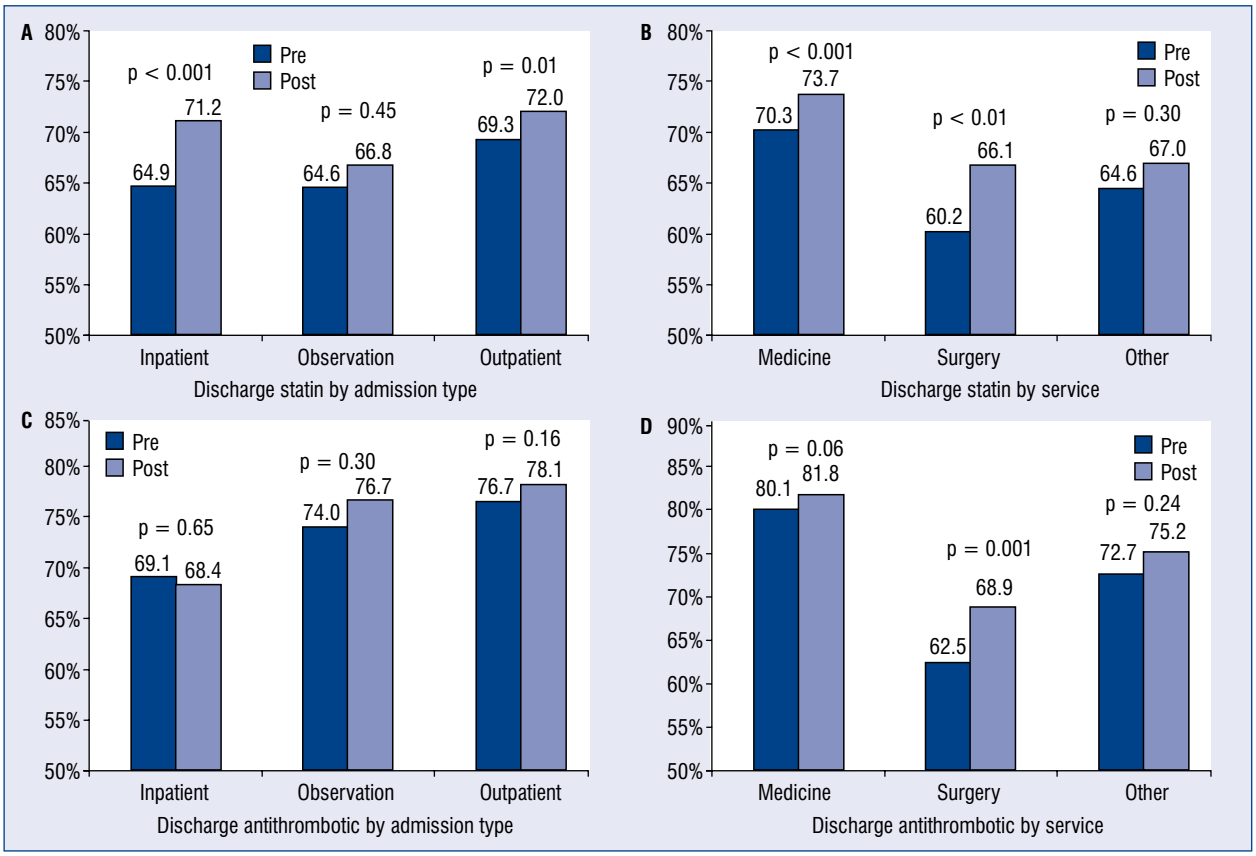

Figure 2. Rates of guideline-directed medical therapy on discharge by admitting service and admission type. Distribution of discharge statin pre- and post-best practice alert implementation by admission type (**A**) and admitting service (**B**). Distribution of discharge antithrombotic pre- and post-best practice alert implementation by admission type (**C**) and admitting service (**D**).

post-BPA cohorts, respectively ($p < 0.001$). There were 4.4% and 5.1% new statin prescriptions at discharge compared to admission in the pre- and post-BPA cohorts, respectively ($p = 0.08$).

Table 2. Multivariable regression for predictors of discharge statin or antithrombotic agent.

	Statin prescribing at hospital discharge		Antithrombotic prescribing at hospital discharge	
	β (SEM)	P	β (SEM)	P
Age [year]	0.02 (0.00)	**< 0.001**	0.03 (0.00)	**< 0.001**
Sex: Male (vs. Female)	0.53 (0.04)	**< 0.001**	0.64 (0.05)	**< 0.001**
Post-BPA implementation (vs. Pre-BPA implementation)	0.19 (0.04)	**< 0.001**	0.17 (0.05)	**< 0.001**
Patient class: Inpatient (vs. All other patient classes as control)	–0.05 (0.05)	0.32	0.14 (0.05)	**< 0.001**
Service: Cardiology (vs. All other services as control)	0.89 (0.05)	**< 0.001**	1.72 (0.06)	**< 0.001**
Service: Medicine (vs. All other services as control)	0.35 (0.04)	**< 0.001**	0.67 (0.05)	**< 0.001**

*Adjusted for age, sex, admission time relative to BPA implementation (pre- or post-BPA implementation), patient class and admitting service; BPA — best practice alert; SEM — structural equation modeling

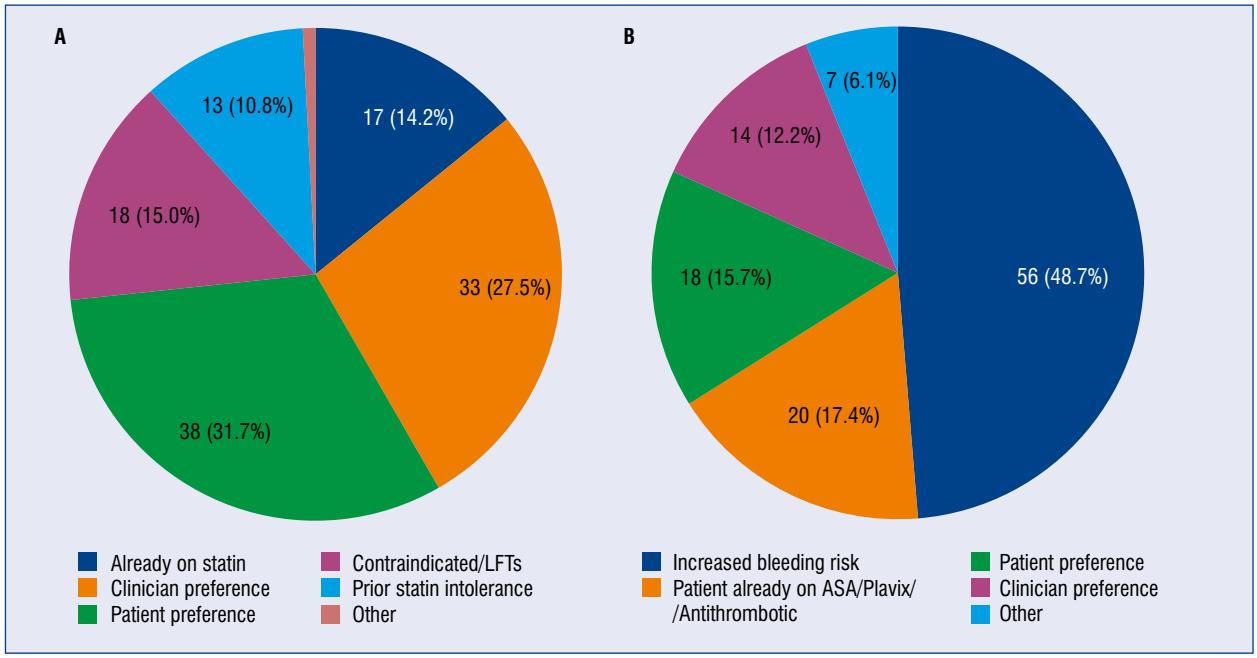

Figure 3. Reasons clinicians dismissed best practice alert recommendations; **A.** Statin best practice alert (BPA): Reasons clinicians disregarded the BPA; **B.** Antithrombotic BPA: Reasons clinicians disregarded the BPA; ASA — acetylsalicylic acid; LFT's — liver function tests.

After multivariable regression, older age, male sex, admission post-BPA implementation, and admission to a cardiology or medicine service were associated with an increased odds of discharge on a statin or antithrombotic agent for ASCVD (Table 2).

During the course of the study, the BPA was activated during 1,117 discharges to prompt providers to prescribe statins and 1,067 discharges to prompt providers to prescribe antithrombotic agents. Providers dismissed the BPA over 80% of the time; it changed prescribing behavior in a minority of cases (8%). Reasons for the BPA being dismissed are listed in Figure 3. Clinician or patient preferences were leading justifications for failure to discharge patients on a statin. Increased bleeding risk was the leading justification for failure to discharge patients on an antithrombotic agent.

Discussion

Despite the impressive cardiovascular advances of our time, limitations persist in seemingly simple factors such as achieving optimal medical therapy and the implementation of lifestyle modification to promote cardiovascular health [16]. This quality improvement initiative at our institution illustrates a straightforward, cost-effective mechanism whereby medical centers with EHR capabilities can modestly improve compliance with GDMT and provide patient-centered educational materials at the critical juncture of hospital discharge. This type of initiative may help overcome health system, provider and patient factors that frequently stand in the way of health improvement [16].

After implementation of our initiative, we observed a statistically significant, albeit modest, increase in provider compliance with GDMT; specifically, a 4.0% increase was identified in discharge prescriptions for statins, a 3.6% increase in high-intensity statins and 3.1% increase in antithrombotic agents in the cohort post-BPA implementation. Moreover, significant increases in discharge statin rates were noted among inpatients admitted to a medicine or surgical service. The intervention also had an impact in patients undergoing ambulatory procedures as well, even though the window for medical optimization prior to discharge was brief.

Unfortunately, in this study providers dismissed the BPA recommendations over 80% of the time, and the BPA impacted prescribing behavior in only 8% of cases. While we were able to collect broad information regarding the reasons that the BPA was dismissed by discharging providers (Fig. 3), future work at our institution will aim to clarify the etiologies of "clinician preference" and "patient preference" in order to identify additional interventions to improve compliance with GDMT in the hospital discharge process. It was suspected that some responses to the BPA may have been a result of alarm fatigue. The constant inundation of EHR alerts may drive providers to bypass the alerts in order to complete the remainder of the workflow for patient care. Institutions may need to prioritize which alerts are essential and limit others that may impede care.

While more limited in scope and duration, our institution's quality initiative shares similarities with the impressive Intermountain Health System's "Hospital-Based Discharge Medication Program" for cardiovascular disease implemented in the early 2000's at all ten Intermountain hospitals. These investigators were able to achieve upwards of 90% compliance with GDMT and saw significant decreases in the relative risk for death at 1 year as well as readmission at 30 days [17]. One key difference that might account for the high compliance and success of the Intermountain program was that discharge-planning nurses were required to directly contact an attending or resident physician if an appropriate medication was not prescribed — essentially creating a 'hard stop' during the discharge process until the medication was prescribed or a specific contraindication was documented. Future iterations of our quality initiative could include a similar hard stop in the discharge process to more effectively influence discharge providers' prescribing behaviors.

The present study is limited by its observational, non-randomized, single-center design. Although the overall effect of the intervention was small and must be balanced against other competing factors such as alarm fatigue and provider frustration, this study demonstrates the feasibility of a simple intervention to increase provider adherence to prescribe GDMT. Refinement in patient selection or the addition of potential 'hard stops' for providers in the discharge process ('obstructive intervention') may further enhance the impact of BPAs. Additionally, a relatively short duration of time for analysis was utilized; further trends in prescribing behavior and compliance to GDMT might be clarified with a longer period of follow-up post-BPA implementation. To better ascertain the downstream effects of our simple EHR-based initiative, we intend to investigate changes in future hospital cardiovascular readmission rates. Lastly, although we were able to successfully implement a mechanism for discharging patients with educational materials and resources, we were unable to directly link improvements in lifestyle, cardiovascular risk factors or medication use to these educational materials.

Conclusions

In summary, with a simple, cost-effective EHR-based quality initiative we were able to demonstrate a modest increase in compliance with GDMT for ASCVD patients and improve the quality of care delivered at hospital discharge at a large academic medical center. As demonstrated in the current study, quality improvement programs are feasible and may be easily implemented to significantly increase adherence to GDMT. Improvements in GDMT adherence may pave the way for reductions in cardiovascular readmission rates and mortality, thereby reducing the tremendous burden of cardiovascular disease [18, 19].

Conflict of interest: None declared

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Clinical characteristics and prognosis of myocardial infarction with non-obstructive coronary arteries: A prospective single-center study

Javier Lopez-Pais[1, 2, 3], Bárbara Izquierdo Coronel[3], David Galán Gil[3], Maria Jesús Espinosa Pascual[3], Blanca Alcón Durán[3], Carlos Gustavo Martinez Peredo[3, 4], Carlos Moreno Vinués[3], Paula Awamleh García[3], Jose Ramón Gonzalez-Juanatey[1, 2], Javier Muñiz García[2, 5, 6], Joaquín Jesús Alonso Martín[3]; on behalf of IMACORN Investigators

[1]Cardiology Department, Hospital Clínico Universitario de Santiago de Compostela, Santiago de Compostela, Spain
[2]Centro de Investigación Biomédica en Red Cardiovascular (CIBERCV), Spain
[3]Cardiology Department, Hospital Universitario de Getafe, Madrid, Spain
[4]Cardiology Department, CHR Mons-Hainaut, Mons, Belgium
[5]Universidade da Coruña, Spain
[6]Instituto de Investigación Biomédica de A Coruña (INCIBIC), Spain

Abstract

Background: *A definition of myocardial infarction with non-obstructive coronary arteries (MINOCA) was published by European Society of Cardiology in 2016. The aim of this study is to analyze the clinical profile and prognosis of these patients in a prospective single-center study and compare it with the literature data.*

Methods: *During a 3-year period, information from every consecutive MINOCA patient was gathered (n = 109). It was then compared with 412 contemporaneous patients with myocardial infarction and obstructive coronary arteries (MIOCA). Univariate and multivariate analyses were performed. Prognosis analysis was adjusted by age and cardiovascular risk factors (CVRF).*

Results: *MINOCA represented 16.9% of the total of patients admitted for myocardial infarction (MI). Compared with MIOCA, they had more psychosocial disorders (22.9% vs. 10.7%; p < 0.01) and more pro-inflammatory conditions (34.9% vs. 14.0%; p < 0.01). Atrial fibrillation was twice as frequent in MINOCA (14.7% vs. 7.3%; p = 0.016). Predictors of MINOCA were as follows: female gender, absence of diabetes, absence of tobacco use, tachycardia, troponin above 10 times the 99th percentile, and pro-inflammatory conditions. Median follow-up was 17.3 ± 9.3 months. Major adverse cardiovascular events (MACE; a composite of a recurrence of acute MI, transient ischemic attack/stroke, or death from cardiovascular cause and death from any cause) occurred in 10.8% of the MINOCA group as compared with 10.7% in the MIOCA group (hazard ratio [HR] 1.19, 95% confidence interval [CI] 0.58–2.45; p = 0.645). Cardiovascular re-admission rates were higher in the MINOCA group: 19.8% vs. 13.9% (HR 1.85; CI 1.06–3.21; p = 0.030).*

Conclusions: *The frequency of MINOCA is high, with fewer CVRF, and it is linked to atrial fibrillation, psychosocial disorders, and pro-inflammatory conditions. Mid-term prognosis is worse than previously thought, with a similar proportion of MACE as compared to MIOCA, and even a higher rate of cardiovascular re-admissions.* (Cardiol J 2022; 29, 5: 798–806)

Key words: myocardial infarction with non-obstructive coronary arteries (MINOCA), prognosis, definition, proinflammatory, atrial fibrillation

Address for correspondence: Javier Lopez-Pais, MD, Cardiology Department. Hospital Clínico Universitario de Santiago de Compostela, Rúa da Choupana s/n, 15703, Santiago de Compostela, A Coruña, Spain, tel: 0034639656529, e-mail: javierlopezpais@gmail.com

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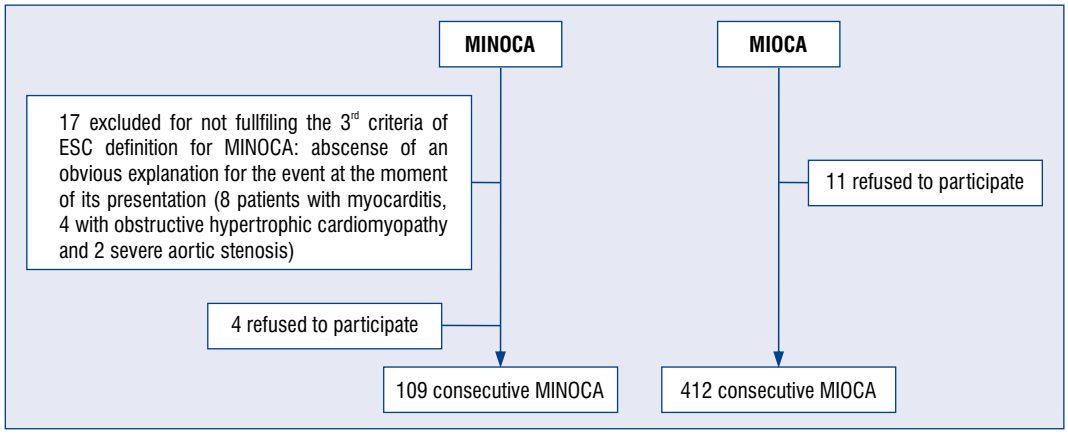

Figure 1. Formation of the cohorts; MINOCA — myocardial infarction with non-obstructive coronary arteries; MIOCA — myocardial infarction with obstructive coronary arteries; ESC — European Society of Cardiology.

Introduction

Coronary atherosclerosis and its complications play a crucial role [1] in the majority of acute coronary syndromes. Nevertheless, there is a subgroup of patients with acute myocardial infarction (AMI) in which coronariography shows non-obstructive coronary arteries. These patients are denominated under the acronym of MINOCA (myocardial infarction with non-obstructive coronary arteries). In extensive epidemiological studies, they represent between 5% and 14% of all AMIs [2–6]. This entity affects younger patients with fewer cardiovascular risk factors (CVRF), mainly women [3, 6, 7], and in some cases these were related with psychosocial disorders [8, 9]. Its prognosis remains controversial [2–5, 10–14], as well as its optimal treatment [4, 5, 8, 15]. The only solid recommendation is to treat the specific physiopathological mechanism when it can be identified. Clinical conditions predicting major adverse cardiovascular events (MACE, a composite of a recurrence of AMI, transient ischemic attack [TIA]/stroke, or death from cardiovascular cause and death from any cause) and mortality of MINOCA patients are similar to those already known in patients with AMI and obstructive coronary arteries [16].

In daily practice, MINOCA remains a challenge, with low use of evidence-based medicines [5] due to lack of clear information. The main reason for this is the absence of a standard definition, making comparison between the studies impossible [2, 3, 11, 12] due to the heterogeneity of the inclusion criteria [5, 10, 16, 17]. In 2016 the European Society of Cardiology (ESC) published a Position Paper on MINOCA [4]. It defined it as a "working diagnosis" to start searching the underlying mechanism in each patient. The ESC has clearly and precisely established the criteria for classifying a patient as a MINOCA, which is a remarkable step in this field. This definition is the one used in recent ESC guidelines [18] and consensus documents, including the 4th Universal Definition of Myocardial Infarction [19].

The aim of this prospective single-center study is to analyze the clinical profile, predictors, and prognosis of MINOCA based on the ESC criteria compared to patients with AMI and obstructive coronary arteries.

Methods

A prospective analytical study of cohorts performed in a University General Hospital that covers a population of 220,000 inhabitants.

Population of the study

All consecutive patients admitted for AMI during a 3-year period (from 1st January 2016 to 31st December 2018) were recorded (Fig. 1). Two cohorts were made: one with those who fulfilled the MINOCA criteria (Table 1) and the other one with the remaining AMI patients. MINOCA was defined according to the ESC Position Paper on MINOCA [4]: AMI according to the 3rd Universal Definition of Myocardial Infarction (which equals to type 1 MI in the 4th Universal Definition of Myocardial Infarction) [19, 20]; and coronary arteries without significant angiographic obstruction (less than < 50% of stenosis). In addition to this, there could not be any other obvious explanation for the event at the moment of its presentation.

Table 1. Inclusion and exclusion criteria for myocardial infarction with non-obstructive coronary arteries (MINOCA) according to European Society of Cardiology position paper.

Inclusion criteria
AMI criteria
Positive cardiac biomarker (preferably cardiac troponin) defined as a rise and/or fall in serial levels, with at least one value above the 99th percentile upper reference limit
+
Corroborative clinical evidence of infarction shown by at least one of the following: — Symptoms of ischemia — New or presumed new significant ST-T changes or new LBBB — Development of pathological Q waves — Imaging evidence of new loss of viable myocardium or new RWMA — Intracoronary thrombus evident on angiography or at autopsy
Non-obstructive coronary arteries on angiography. This includes both patients with: — Normal coronary arteries (no stenosis or < 30%) or — Mild coronary atheromatosis (stenosis > 30% but < 50%)
Exclusion criteria
Alternative cause for the acute presentation — Suspected myocarditis at admission — Suspected pulmonary thromboembolism
Acute myocardial injury Elevated troponin value above the 99th percentile (with a rise and/or fall of troponin value) but without clinical or electrocardiographic evidence of acute myocardial ischemia

LBBB — left bundle branch block; RWMA — regional wall motion abnormality

This point was confirmed in every case during a thorough review carried out by trained cardiologists. Patients who suited the new definition of myocardial injury [19] were excluded.

As a control group, we used the second cohort consisting of 412 consecutive patients admitted with AMI and obstructive coronary arteries (MIOCA) during the same period.

Based on previous data, around 10% of AMI patients will be MINOCA. Above 400 patients will be sufficient if we assume a rate of events in the first year of 13% in MIOCA and 5% in MINOCA (alpha error of 0.05 and power of 0.80).

All patients provided written informed consent. The study was approved by the institutional review board and followed the tenets of the Declaration of Helsinki.

Variables

Standardized forms were used to set up the database, including demographic information, epidemiological data, and relevant clinical information. Socio-economic aspects that could act as emotional stress modulators were also registered, as well as psychosocial disorders (a compound of previously diagnosed psychiatric disease {According to Diagnostic and Statistical Manual of Mental Disorders, fifth edition, [21]} and/or chronic anxiety treatment) and migraine. Data involving pro-inflammatory conditions were also collected: the presence of active cancer, autoimmune diseases, or the fact that AMI was an intercurrent complication during hospitalization for another pathology. The main laboratory results (Siemens Healthcare Diagnostic, Erlangen, Germany) were peak creatinine kinase, troponin T, and C-reactive protein.

According to current guidelines and previous reports [22], optimal medical treatment at discharge was considered when patients simultaneously received antiplatelets, statins, and angiotensin-converter enzyme inhibitors or angiotensin receptor blockers.

All in-hospital complications and death from any cause were registered. Follow-up analysis included the following: MACE, time to first readmission, and death from any cause. Follow-up data were based on clinical visits, institutional database, or telephone interviews.

Statistical analysis

Continuous variables are presented as means and standard deviations or as medians with interquartile range. Categorical variables are provided with percentages. Pearson χ^2 or Student's t-test and their non-parametric equivalent were used depending on the variable type. A two-sided p value of less than 0.05 was considered statistically significant. Characteristics at admission with a p value < 0.01 in the univariable comparison were included in a logistic regression model (as a block: enter method) to determining the presence of early predictors of MINOCA.

Survival analysis with Kaplan-Meier (using long-rank) was performed for each follow-up event between MINOCAs and AMI-coronary artery disease. Prognosis analysis was developed with multiple Cox regression models adjusted depending on age and CVRF. Odds ratios and hazard ratios (HR) are reported with 95% confidence intervals (CI).

Results

Clinical characteristics and in-hospital evolution

During the recruitment period, 644 consecutive patients were diagnosed with AMI. Coronariography was performed in 521 cases. Among those, 109 fulfilled the 2016 ESC definition of MINOCA, representing 16.9% of the AMI admitted at the hospital. The most common underlying mechanism in MINOCA was stress myocardiopathy (25.9%). In 13.4% plaque disruption was identified, 9.8% had positive vasospasm provocation test, 3.6% presented coronary emboli, and 0.9% coronary dissection. Almost 9% were diagnosed with type 2 AMI. In 30.8% the mechanism remained unclear despite all tests performed. Only 7.1% of the patients initially included in the working diagnosis of MINOCA were finally diagnosed with myocarditis.

Considering that this is the sole hospital for the sanitary population in the area (totaling 220,000), we can estimate an annual incidence of 36.3/MINOCA/year and an annual incidence tax of 0.17 MINOCA per 1000 inhabitants/year.

Table 2 summarizes baseline characteristics of both cohorts. Patients with MINOCA compared to those with MIOCA were more frequently women (51.4% vs. 21.8%; $p < 0.001$) and with a better cardiovascular risk profile: less diabetes (23.9% vs. 35.6%; $p = 0.020$) and lower smoking rates (40.3% vs. 65.5%; $p < 0.001$). Regarding the patients' age, MINOCA patients were non-significantly younger (64.6 ± 14.9 years and 66.7 ± 13.5 years, respectively; $p = 0.171$).

The prevalence of pro-inflammatory conditions (compound of autoimmune diseases, active cancer, and being AMI a complication intercurrent with hospitalization for another pathology) was higher in the MINOCA group: 34.9% vs. 14.0%; $p < 0.001$. The relationship was maintained with autoimmune diseases (17.4% vs. 8.0%; $p < 0.004$) and active cancer (10.1% vs. 3.4%; $p < 0.004$) on their own.

The atrial fibrillation rate was twice as frequent in the MINOCA group compared to the MIOCA group (14.7% vs. 7.3%; $p = 0.016$). Psychosocial disorders and migraine were higher in the MINOCA group: 22.9% vs. 10.7% ($p = 0.001$) and 10.1% vs. 4.1% ($p = 0.015$), respectively.

The main data regarding hospitalization are shown in Table 3. MINOCA patients had higher heart rate at presentation (89.2 ± 27.1 vs. 79.1 ± ± 17.7; $p < 0.001$). The main symptom was angina in 73.9% of MINOCA patients as compared with 82.8% in the MIOCA group ($p = 0.027$). MINOCA patients less frequently had an ischemic electrocardiogram pattern (new or presumed new significant ST-T changes or new left bundle branch block; 61.1% vs. 72.7%; $p < 0.020$). As Table 2 shows, cardiac necrosis biomarkers were lower in the MINOCA group. Left ventricular dysfunction was present in 33.8% of MINOCA group as compared to 31.5% of the MIOCA group ($p = 0.659$). None of the MINOCA patients was revascularized; regarding MIOCA group, 93.9% underwent percutaneous coronary intervention and 6.1% had bypass surgery.

In-hospital complications (re-infarction, major bleeding, stroke, cardiorespiratory arrest, pulmonary edema, or shock) occurred in 13.8% of the MINOCA patients and in 17.6% of the MIOCA group ($p = 0.335$). In-hospital mortality was non-significantly lower in MINOCA patients (0.9% vs. 3.4%; $p = 0.167$).

At discharge, double antiplatelet treatment was prescribed in 62.0% of MINOCA patients, as compared with 99.7% of the MIOCA patients ($p < 0.001$). There were also differences in the prescription of beta-blockers (60.2% vs. 86.8%, $p < 0.001$), angiotensin convertase enzyme inhibitors/angiotensin II receptor antagonists (59.3% vs. 78.2%, $p < 0.001$), and statins (58.3% vs. 95.7%, $p < 0.001$). Anticoagulation prescription was higher in the MINOCA group (22.2% vs. 10.1%; $p < 0.001$).

Predictors of MINOCA at admission

Six characteristics that could be determined at admission had independent association with MINOCA and can be used as early predictors: female gender, absence of diabetes, absence of tobacco use, tachycardia (100 bpm or above), troponin above 10 times 99-percentile (usual laboratory threshold), and the presence of a pro-inflammatory condition (autoimmune diseases, or active cancer, or AMI being a complication during hospitalization for another pathology). Details of the analysis are represented in Table 4.

Prognosis

Median follow-up was 17.3 ± 9.3 months. The time-to-event analysis is summarized in Figure 2. MACE occurred in 10.8% of the MINOCA group as compared with 10.7% in the MIOCA group (HR of 1.19, 95% CI 0.58–2.45; $p = 0.645$). Regarding individual components, cardiovascular mortality was non-significantly lower in the MINOCA group (2.8% vs. 5.1%; HR 0.54, 95% CI 0.12–2.36). Also, they had a non-significantly higher rate of TIA/ /stroke (3.0% vs. 0.8%; HR 2.89, CI, 0.52–16.13)

Table 2. Demographic profile, cardiovascular risk factors, proinflammatory conditions, and other comorbidities comparing both cohorts.

	MINOCA (n = 109)	MIOCA (n = 412)	p
Basal characteristics			
Age [years]	64.6 ± 14.9	66.7 ± 13.5	0.171
Female gender	56/109 (51.4)	90/412 (21.8)	< 0.001
Cardiovascular risk factors			
Hypertension	67/109 (61.5)	256/412 (62.1)	0.830
Diabetes	26/109 (23.9)	146/412 (35.6)	0.020
Dyslipidemia	49/109 (45.2)	223/412 (54.1)	0.090
Tobacco use	44/109 (40.3)	270/412 (65.5)	< 0.001
Pro-inflammatory conditions	38/109 (34.9)	58/412 (14.0)	< 0.001
Active cancer	11/109 (10.1)	14/412 (3.4)	0.004
Autoimmune diseases	19/109 (17.4)	33/412 (8.0)	0.004
AMI while hospitalization for other pathology	8/109 (7.3)	10/412 (2.4)	0.13
Other comorbidities			
Atrial fibrillation	16/109 (14.7)	30/412 (7.3)	0.016
Psychosocial disorders	25/109 (22.9)	44/412 (10.7)	0.001
Migraine	11/109 (10.1)	17/412 (4.1)	0.015

AMI — acute myocardial infarction; MINOCA — myocardial infarction with non-obstructive coronary arteries; MIOCA — myocardial infarction with obstructive coronary arteries

Table 3. Characteristics at admission and in-hospital complications.

	MINOCA (n = 109)	MIOCA (n = 412)	P
At admission			
Heart rate [bpm]	89.2 ± 27.1	79.1 ± 17.7	< 0.001
Systolic arterial pressure [mmHg]	140.7 ± 28.0	143.7 ± 30.1	
ST-segment elevation	26/109 (24.1)	166/412 (40.8)	0.001
ST-segment decrease or inversion of T wave	66/109 (61.1)	295/412 (72.7)	0.020
Laboratory			
Troponin T HS [ng/mL]	743.1 ± 1808.6	2856.2 ± 0	< 0.001
Hemoglobin [g/dL]	13.5 ± 2.1	14.2 ± 1.8	0.003
Creatinine [mg/dL]	1.1 ± 0.9	1.2 ± 1.1	0.467
Echocardiogram			
Left ventricular dysfunction	37/109 (33.8)	130/412 (31.5)	0.659
Severe left ventricular dysfunction	8/109 (7.4)	20/412 (4.5)	0.313
Moderate-severe valve disease	7/109 (6.4)	20/412 (4.8)	0.509
Pulmonary hypertension	5/109 (4.6)	27/412 (6.6)	0.436
In-hospital complications	15/109 (13.8)	72/412 (17.6)	0.335
Reinfarction	3/109 (2.8)	16/412 (3.9)	0.562
Major bleeding	2/109 (1.8)	13/412 (3.2)	0.453
Acute cerebrovascular accident	3/109 (2.8)	7/412 (1.7)	0.487
Cardio-respiratory arrest	0/109 (0.0)	15/412 (3.7)	0.042
Acute pulmonary edema	8/109 (7.3)	24/412 (5.9)	0.579
Cardiogenic shock	5/109 (4.6)	33/412 (8.1)	0.211
Mechanical complications	0/109 (0.0)	2/412 (0.5)	0.463
In-hospital mortality	1/109 (0.9)	14/412 (3.4)	0.167
Duration of hospitalization (days)	8.89 ± 13.1	6.91 ± 6.0	0.025

Severe left ventricle dysfunction is defined as ejection fraction < 30%; MINOCA — myocardial infarction with non-obstructive coronary arteries; MIOCA — myocardial infarction with obstructive coronary arteries

Table 4. Early predictors of myocardial infarction with non-obstructive coronary arteries by multivariable analysis.

	Odds ratio	95% CI	p
Female gender	2.60	1.50–4.51	0.001
Tobacco use	0.49	0.29–0.83	0.008
Diabetes	0.44	0.25–0.76	0.004
Pro-inflammatory conditions	2.32	1.33–4.05	0.003
Tachycardia at admission	2.32	1.27-–4.24	0.006
Troponin T peak > 10×p99	2.53	1.35–4.73	0.004

CI — confidence interval; pro-inflammatory conditions — active cancer, autoimmune diseases or acute myocardial infarction during other pathology hospitalization; 10×p99 — 10 times 99th percentile

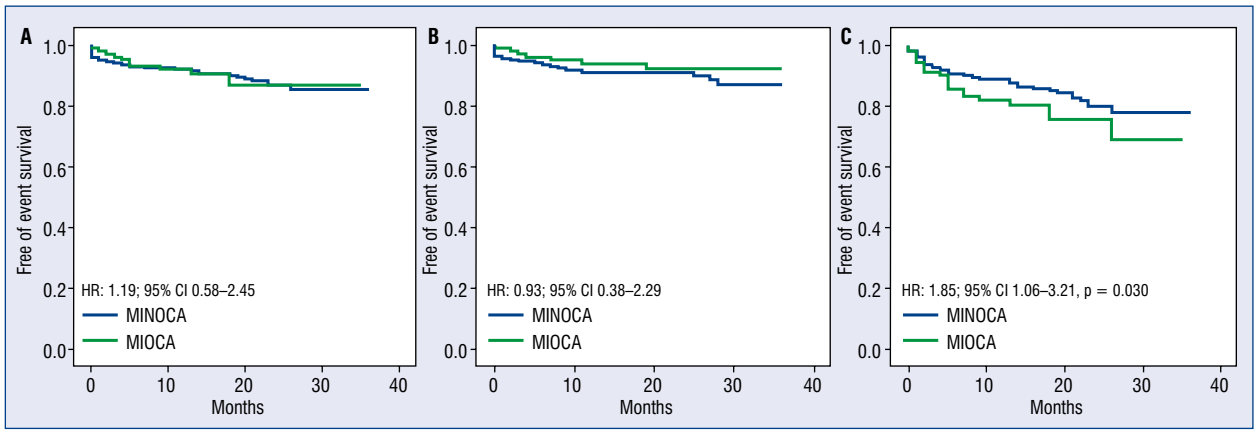

Figure 2. Kaplan-Meyer curves comparing both cohorts: myocardial infarction with non-obstructive coronary arteries (MINOCA) and myocardial infarction with obstructive coronary arteries (MIOCA); **A.** Major adverse cardiovascular events (cardiovascular death, transient ischemic attack/stroke, or re-infarction); **B.** All-cause mortality; **C.** Cardiovascular re-admissions; HR —hazard ratio adjusted by age and cardiovascular risk factors; CI — confidence interval.

and re-infarction (5.9% vs. 4.7%; HR 1.61, 95% CI 0.60–4.29). Cardiovascular re-admission rates were higher in the MINOCA group: 19.8% as compared with 13.9% in the MIOCA group (HR 1.85, 95% CI 1.06–3.21; p = 0.030).

Death from any cause occurred in 6.9% of MINOCA patients as compared with 9.3% in the MIOCA group (HR 0.93, 95% CI 0.38–2.29). The proportion of all-cause re-admission rates tended to be higher in the MINOCA group: 33.7% vs. 32.7% (HR 1.45, 95% CI 0.94–2.25; p = 0.097). Details regarding these analyses are provided in Table 5.

At the 1-year interview, 1.0% of MINOCA patients referred stable angina compared with 2.4% of the MIOCA patients (p = 0.337); at that moment, dyspnea worse than New York Heart Association II was present in 6.1% of the MINOCA vs. 9.6% of the MIOCA group (p = 0.268).

Discussion

The impact of MINOCA on daily clinical practice is high, representing 16.9% of all AMI in which coronariography is performed. This proportion is slightly higher than previously described [2, 3, 10–12] and may be related to the use of new ultra-sensitive troponin assay, even though cases of myocardial injury were not included. Improved early screening techniques and increased awareness are leading to increased MINOCA diagnoses [23].

This job is in line with previous studies by checking that patients with MINOCA are more frequently women [24] and have a better cardiovascular risk profile compared with MIOCA patients [3, 6, 7, 10, 12]. An interesting new point here is that the prevalence of atrial fibrillation is higher in

Table 5. Main findings at 12-month follow-up survival analysis adjusted by age and cardiovascular risk factors (hypertension, dyslipidemia, diabetes, and tobacco).

	MINOCA	MIOCA	HR	95% CI	P
MACE	10.8%	10.7%	1.19	0.58–2.45	0.645
CV re-admission	19.8%	13.9%	1.85	1.06–3.21	0.030
CV mortality	2.8%	5.1%	0.54	0.12–2.36	0.410
Re-infarction	5.9%	4.7%	1.61	0.60–4.29	0.341
TIA or stroke	3.0%	0.8%	2.89	0.52–16.13	0.226
Total mortality	6.9%	9.3%	0.93	0.381–2.29	0.880
Re-admission	33.7%	32.7%	1.45	0.94–2.25	0.097

CI — confidence interval; CV — cardiovascular; HR — hazard ratio; MACE — major adverse cardiovascular events (infarction, TIA/stroke or CV death); MINOCA — myocardial infarction with non-obstructive coronary arteries; MIOCA — myocardial infarction with obstructive coronary arteries; TIA — transient ischemic attack

MINOCA, a fact that could be related to coronary emboli as the physiopathological explanation in some cases.

Also, psychiatric diseases, migraine, and pro-inflammatory conditions are more frequent in the MINOCA group than in MIOCA. Previous studies proposed a connection between psychiatric diseases and MINOCA [25], specifically with takotsubo syndrome [8]. This was also checked in a sub-analysis of our group in which, even after excluding takotsubo syndrome patients from the analysis, MINOCA and psychosocial disorders remained associated [9]. Different mechanisms could explain this association: the most reasonable of which is the impact of emotional stress in sympathetic regulation [26], being catecholamine levels a fundamental player in the endothelial function regulation [27]. Direct catecholamine toxicity on cardiomyocytes has also been proposed [28]. Nociceptive mechanisms of migraine are thought to be in relation with vascular tone dysregulation [29], one of the feasible mechanisms underlying MINOCA.

A higher presence of pro-inflammatory conditions in MINOCA has recently been described [7] and points in the direction of new evidence about the interrelation between the immune system and ischemic heart disease. Some interesting studies have also been published in this field, like the CANTOS trial [30], reflecting the impact of immunomodulator therapies in cardiovascular risk; or the relation between influenza infection and AMI [31]. As for MINOCA, a hypersensitivity-associated AMI has also been described, known as Kounis syndrome [32].

It has been postulated that MINOCA patients have a better prognosis than MIOCA patients [3]. However, given the heterogeneity of the analyzed groups in previous studies, there are significant differences regarding the prognosis (between 3% and 8% of 1-year mortality) [3, 6, 10–12, 33]. One of the latest works [25] described a 1-year mortality of 4.7% while in other specific types of presentation (ST-segment elevation MINOCA) 1-year mortality was 7% [10]. In Spain [6] there was lower mortality at 3-year follow-up in patients with non-ST-segment elevation AMI and non-significant stenosis compared with those with significant stenosis, while in a more recent work [12] the described mortality was similar to those patients with one-vessel disease. Considerable differences in the inclusion criteria of these works should be taken into account.

This prospective study based on the standards of MINOCA definition shows that MINOCA prognosis could be worse than was previously thought. Despite a lower CVFR charge, MINOCA did not differ from MIOCA in terms of MACE events and had a higher number of cardiovascular re-hospitalizations. There was an excess of mortality in the MIOCA group, but, conversely, MINOCA patients had more re-infarction and TIA/stroke during follow-up. MINOCA may encompass milder mechanisms that confer a better prognosis, but could also lead to misdiagnosis in the index episode.

The daily importance of MINOCA is high, not only because of its incidence, but also for all the complex studies it requires for its correct characterization in order to adjust the proper treatment (intravascular imaging, magnetic resonance) [34, 35]. This causes a longer hospitalization and, consequently, an increment in the economic costs. Studies like this one would help to know better

the role of the working diangnosis of MINOCA in the future as well as helping to reveal independent predictors in these patients.

Limitations of the study

Apart from the inherent problems of an observational single-center study, this work has other limitations that must be outlined to provide a correct interpretation of the results: (1) It was conducted in a center with a modest recruitment capacity, so the recruitment period had to be prolonged for three years. This could lead to a reduction in the power of some analyses; (2) We had some financial limitations for performing exhaustive intravascular imaging. That affects the characterization of MINOCA patients whose mechanism was the transient complication of the atheroma plaque [35], and some of them could have been erroneously classified as an unknown mechanism; (3) The same argument applies to magnetic resonance (performed in only 34.3% of MINOCA patients). Despite this, economic restrictions are unfortunately a common factor nowadays, and this can reflect the daily clinical practice for many of hospitals. This improves the applicability of the results presented. Including all consecutive MINOCA patients may mitigate in part this limitation.

Conclusions

MINOCA represents a considerable proportion of all AMIs. Its clinical presentation is very similar to MIOCA, so it reinforces the idea of considering it as a "working diagnosis". These results are in agreement with most previous reports. However, mid-term prognosis may be worse than previously thought.

Patients with MINOCA have lower charge of traditional risk factors, but psychosocial disorders, pro-inflammatory conditions, atrial fibrillation, and migraine are more frequent among them. This study complements the study of MINOCA and provides some new data in this field that could improve the future management of these patients.

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Clinical outcomes of cryoballoon ablation for pulmonary vein isolation: Impact of intraprocedural heart rhythm

Bruno Reissmann[1, 2], Christian-H. Heeger[2, 3], Karena Opitz[2], Michael Schlüter[4], Peter Wohlmuth[4], Laura Rottner[1, 2], Thomas Fink[2, 3], Jin-Hong Gerds-Li[5], Shibu Mathew[2], Christine Lemes[2], Tilman Maurer[2], Feifan Ouyang[2], Karl-Heinz Kuck[2], Andreas Rillig[1, 2], Doreen Schöppenthau[5]*, Andreas Metzner[1, 2]*

[1]Department of Cardiology, University Heart Center Hamburg, Germany
[2]Department of Cardiology, Asklepios Klinik St. Georg, Hamburg, Germany
[3]University Heart Center Lübeck, Germany
[4]Asklepios Proresearch, Hamburg, Germany
[5]Department of Internal Medicine and Cardiology, German Heart Institute, Berlin, Germany

Abstract

Background: *The current study sought to assess the impact of the intraprocedural heart rhythm (sinus rhythm [SR] vs. atrial fibrillation [AF]) on acute procedural characteristics, durability of pulmonary vein isolation (PVI) and long-term clinical outcomes of cryoballoon (CB) ablation.*

Methods: *A total of 195 patients with symptomatic paroxysmal (n = 136) or persistent AF (n = 59) underwent CB-based PVI. Ablation procedures were either performed in SR (SR group; n = 147) or during AF (AF group; n = 48). Persistent AF was more frequent in the AF group than in the SR group (62% vs. 20%). All other patient baseline characteristics did not differ between the two groups.*

Results: *The nadir temperature during the CB applications was significantly lower in the AF group than in patients in the SR group (–49 [interquartile range, –44; –54]°C vs. –47 [–42; –52]°C, p = 0.002). Median procedure and fluoroscopy times as well as the rate of real-time recordings were not different between the two groups. Repeat ablation for the treatment of atrial arrhythmia recurrence was performed in 60 patients (SR: 44 [30%] patients; AF: 16 [33%] patients), with a trend towards a lower rate of pulmonary vein reconnections in the AF group (p = 0.07). There was no difference in 3-year arrhythmia-free survival (p = 0.8).*

Conclusions: *Cryoballoon-based PVI during AF results in lower nadir balloon temperatures and a trend towards a higher durability of PVI as compared to procedures performed in SR. The rate of real-time PVI recordings was not affected by the intraprocedural heart rhythm.* (Cardiol J 2022; 29, 5: 807–814)

Key words: clinical outcomes, cryoballoon ablation, pulmonary vein isolation, intraprocedural heart rhythm

Address for correspondence: Bruno Reissmann, MD, Department of Cardiology, University Heart Center Hamburg, Martinistr. 52, 20246 Hamburg, Germany, tel: +49 (0)40 7410-58320, fax: +49 (0)40 7410-55862, e-mail: b.reissmann@uke.de

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**Shared last authorship*

Introduction

Cryoballoon (CB) ablation has become an established treatment option for patients with atrial fibrillation (AF) [1–4]. The procedural endpoint is electrical isolation of the pulmonary veins (PV) [5]. Recent data indicate improved durability of pulmonary vein isolation (PVI) after CB ablation than after radiofrequency current (RFC) ablation [6]. Nevertheless, the number of patients requiring repeat ablation because of recurrences of AF — mainly driven by reconnected PV — remains high following either approach [7]. In contrast to point-by-point RFC ablation, the CB does not provide different energy levels, e.g., does not allow the use of higher energy settings at locations of poor tissue-catheter contact, such as the ridge between the left PV and the left atrial appendage. Once the CB has tissue contact at the antral aspect of the targeted PV, cryothermal energy is delivered via the entire distal hemisphere of the balloon. Durable, transmural lesion formation depends on the freeze cycle duration, and, more importantly, on the tissue contact of the CB. Since the latter cannot be measured directly, complete occlusion of the PV, duration of the temperature drop and nadir CB temperature serve as important surrogate parameters [8]. Theoretically, the reduced atrial contractility during AF might result in an enhanced stability of the balloon catheter and thereby, a more effective freeze cycle. However, to date, the impact of the intraprocedural rhythm (sinus rhythm [SR] vs. AF) during CB ablation has not yet been investigated.

The aim of the present study was to assess acute procedural characteristics, durability of PVI in patients with repeat ablation procedures and long-term clinical outcomes of CB ablation performed during AF or in SR.

Methods

Inclusion and exclusion criteria

Patients with symptomatic paroxysmal or persistent AF (as defined by 2016 ESC guidelines [5]) were included in the current study. Exclusion criteria were prior left atrial (LA) ablation procedures, a LA diameter > 60 mm, severe valvular heart disease or contraindications to post-interventional oral anticoagulation. Procedures were performed at two centers (Asklepios Klinik St. Georg, Hamburg, Germany, and German Heart Institute, Berlin, Germany).

The current study constitutes a retrospective analysis based oninstitutional databases. The study was approved by the local ethics boards and performed in accordance with the Declaration of Helsinki of 2013.

Preprocedural management

Transesophageal echocardiography was performed prior to PVI in all patients to rule out intracardiac thrombi and to assess LA diameter. No further pre-procedural imaging was performed.

Intraprocedural management

The intraprocedural management has been described in detail before [4, 9, 10]. In brief, in patients on vitamin K antagonists the procedure was performed under therapeutic international normalized ratio (INR) values of 2–3. Novel oral anticoagulants were stopped the day before the procedure and were later resumed 6 hours post ablation. All procedures were performed under deep sedation using midazolam, sufentanyl and propofol. One or two diagnostic catheters were introduced via the femoral vein and/or the left subclavian vein and were positioned within the coronary sinus and/or along the His bundle. A single transseptal puncture was performed via the femoral vein under fluoroscopic guidance, using a modified Brockenbrough technique and an 8.5 French (F) transseptal sheath (SL1, St. Jude Medical Inc., St. Paul, USA). After transseptal puncture, heparin boluses were administered in 30-minute intervals targeting an activated clotting time of ≥ 300 s. Selective angiographic visualization by dye injections or rotational angiography was performed to identify the individual PV ostia.

Cryoballoon-based PVI

The 28-mm second-generation CB was utilized exclusively in this study. The transseptal sheath was exchanged over a guidewire for a 12 F steerable sheath (FlexCath AdvanceTM, Medtronic, Inc.), through which the CB was advanced into the LA. Guiding of the CB to the target PV was performed over a 20-mm inner-lumen circular mapping catheter (Achieve™, Medtronic, Inc.) and complete occlusion of the PV ostium was verified by contrast injection through the central lumen of the inflated CB.

Patients were treated based on a "time-to--isolation" guided ablation protocol, i.e., after real-time verification of PVI, freezing was continued for an additional 120 s. In cases where the "time-to--isolation" could not be recorded, the freeze-cycle duration was set at 180 s; no additional bonusfreeze cycle was applied after successful PVI [9]. In patients undergoing CB ablation during AF, electrical

cardioversion was performed at the end of the procedure to restore SR.

An esophageal temperature probe (Sensitherm, St Jude Medical, Inc.; or Circa, Circa Scientific, Inc.) was inserted and positioned according to the individual CB position to provide esophageal temperature monitoring. The intraluminal esophageal temperature cut-off was set at 15°C [11].

During CB ablation along the septal PV, continuous phrenic nerve (PN) pacing was performed using a diagnostic catheter positioned in the superior vena cava (6 F, InquiryTM, St. Jude Medical, Inc.). PN capture was monitored by tactile feedback of diaphragmatic contraction by placing the operator's hand on the patient's abdomen. In addition, the continuous motor action potential was monitored and delivery of the refrigerant was stopped immediately if weakening or loss of diaphragmatic movement was noted or the amplitude of the continuous motor action potential decreased by 30% [12, 13].

Postprocedural care

Transthoracic echocardiography was performed in all patients to rule out a pericardial effusion. All patients were treated with proton-pump inhibitors for 4–6 weeks. Low molecular-weight heparin was administered in patients on vitamin K antagonists and an INR < 2.0 until a therapeutic INR of 2–3 was reached. Anticoagulation was continued for at least 3 months, and thereafter based on the individual CHA2DS2-VASc score. Previously ineffective antiarrhythmic drugs were continued for 3 months.

Follow-up

Following a blanking period of 3 months, patients completed outpatient clinical visits at 3, 6 and 12 months and in 6-month intervals thereafter according to our institutional standard; the clinical visits included electrocardiograms (ECGs) and 24 h-Holter ECGs. In patients with an implantable cardiac device with rhythm monitoring, regular device interrogations were additionally performed in order to detect arrhythmia recurrences. Moreover, regular telephone interviews were performed. In case of symptoms suggestive of recurrent arrhythmia, patients were advised to contact the outpatient clinic and subsequent clinical visits were immediately initiated.

Endpoints

The primary endpoints of this investigation were acute procedural characteristics, i.e., nadir balloon temperatures, procedure durations, fluoroscopy times, rate of real-time PVI recordings, and reconnection of initially isolated PV (assessed in patients with repeat ablation for recurrence of AF). Secondary endpoints were a documented recurrence of atrial arrhythmia with a duration of > 30 s outside the 3-month blanking period and complications, e.g., transient ischemic attack, stroke, pericardial tamponade, PN paralysis (PNP), and severe bleeding requiring blood transfusion.

Statistical analysis

All data were evaluated retrospectively. Continuous data are described as mean and standard deviation (SD) if normally distributed; otherwise the median and interquartile range [IQR, first quartile; third quartile] are reported. Categorical data are described with absolute and relative frequencies. Based on a logistic regression model (global test of no regression) baseline variables were simultaneously compared between the two groups.

Differences in procedural data were analyzed with a linear mixed model. Freedom from atrial arrhythmia recurrence was estimated with the Kaplan-Meier method. Differences in recurrence-free survival were analyzed with the log-rank test. All p-values were two-sided and a p-value < 0.05 was considered statistically significant. All calculations were performed with the statistical analysis software R (R Core Team, 2019).

Results

Patients

A total of 195 patients with symptomatic paroxysmal (n = 136) or persistent AF (n = 59) underwent PVI with the 28-mm second-generation CB. Ablation procedures were either performed in SR (n = 147) or during AF (n = 48). Persistent AF was more prevalent in the AF group than in the SR group (62% vs. 20%). All other baseline patient characteristics did not differ between the two groups (Table 1).

Procedural characteristics

In 193/195 patients, all PV were successfully isolated, while in 2 patients of the SR group both right inferior PV and one right superior PV were not isolated due to the occurrence of PNP. The nadir temperature during the freeze cycle applications was significantly lower in patients treated during AF than in patients treated in SR (–49 [IQR, –44; –54]°C vs. –47 [–42; –52]°C, p = 0.002). Median procedure and fluoroscopy times as well as the

Table 1. Baseline patient characteristics.

Characteristics	SR group (n = 147)	AF group (n = 48)
Age [years]	63 [54;70]	66 [55;71]
Male gender	92 (63)	33 (69)
Paroxysmal AF	118 (80)	18 (38)
Persistent AF	29 (20)	30 (62)
CHA_2DS_2-VASc score:		
0	28 (19)	8 (17)
1	37 (25)	8 (17)
2	37 (25)	14 (29)
3	32 (22)	11 (23)
4	8 (5)	5 (10)
5	5 (3)	2 (4)
BMI [kg/m^2]	28 ± 5	27 ± 4
LA diameter [mm]	42 ± 5	45 ± 5
LVEF < 50%	9 (6)	3 (6)
Coronary artery disease	17 (12)	6 (12)
Diabetes mellitus	17 (12)	5 (10)
COPD	9 (6)	2 (4)
Smoker	19 (13)	5 (10)
Arterial hypertension	91 (62)	29 (60)

Values are mean ± standard deviation, median [first quartile; third quartile], or number (%). Presence of persistent atrial fibrillation differ in the two groups. No difference was revealed considering the remaining characteristics (test of no regression: p = 0.713). AF — atrial fibrillation; BMI — body mass index; COPD — chronic obstructive pulmonary disease; LA — left atrium; LVEF — left ventricular ejection fraction; SR — sinus rhythm

rate of time-to-isolation recordings did not differ between the two cohorts. Procedural parameters are given in Table 2.

Periprocedural complications

Procedural complications were two cardiac tamponades requiring pericardiocentesis, an arteriovenous fistula and two groin hematomas with conservative treatment each. PNP occurred in 3 patients resulting in absence of PVI in two right inferior PV and one right superior PV as stated previously. In 1 patient all PV were successfully isolated at the time of PNP. No atrio-esophageal fistula, no symptomatic PV stenosis, no stroke and no procedure-related deaths were observed.

Repeat ablation procedures

Repeat ablation for the treatment of atrial arrhythmia recurrence following the index CB procedure was performed in 60 patients (SR group: 44 [30%] patients; AF group: 16 [33%] patients). Procedures were exclusively performed with the use of RFC guided by 3-dimensional mapping. All patients showed electrical reconnection of at least one initially isolated PV. All PV were successfully re-isolated. There was a trend towards a lower rate of PV reconnections in the AF group without being statistically significant (p = 0.07). Characteristics of PV reconnections during repeat ablation procedures are given in Table 2.

Clinical follow-up

In the SR and the AF group, 1-, 2- and 3-year estimated arrhythmia-free survival was 78% and 75%, 64% and 69%, and 57% and 57%, respectively. The log-rank test did not indicate a significant difference in arrhythmia-free survival between the groups (p = 0.8). Recurrence-free survival is bshown in Figure 1.

Discussion

Main findings

According to available research, the current study represents the first analysis investigating the impact of the intraprocedural heart rhythm during CB-based PVI on procedural characteristics and clinical outcomes. The main findings are: 1) significant lower nadir CB temperatures in patients undergoing PVI during AF than in patients being treated in SR; 2) a trend towards improved durability of PVI performed during AF; and 3) no influence of the basic rhythm on procedure and fluoroscopy times as well as the rate of time-to-isolation recordings during PVI. The 3-year arrhythmia-free survival did not differ between the two groups.

Key factors on efficacious CB ablation

Over the last decade, CB ablation aiming at PVI has become an established treatment for AF. During this time, several predictors of freedom from recurrence of AF and permanent PVI have been identified. As such, the time to PVI (confirmed by real-time recordings), the thaw time, and the nadir temperature of the CB impact PVI durability [8, 14–16]. Each of these parameters represents a surrogate of the balloon-tissue contact and energy transfer, which is still the most relevant aspect in creating durable, transmural cryolesions. The present study provides new insights into the impact of the intraprocedural heart rhythm on procedural parameters and clinical outcomes of CB ablation. One important result is the significantly lower nadir CB temperature in the AF group indicating that the reduced atrial contractility during AF is beneficial for balloon-tissue contact and en-

Table 2. Procedural data.

Characteristics	SR group (n = 147)	AF group (n = 48)	P
Total procedure time [min]	130 [110; 152]	135 [120; 145]	0.497
Fluoroscopy time [min]	18 [14; 25]	20 [16; 24]	0.364
Nadir balloon temperature [°C]:	–47 [–42; –52]	–49 [–44; –54]	0.002
RSPV	–50 [–44; –53]	–52 [–48; –55]	
RIPV	–46 [–41; –49]	–48 [–43; –54]	
LSPV	–47 [–42; –52]	–50 [–43; –56]	
LIPV	–44 [–41; –49]	–48 [–43; –52]	
LCPV	–55 [–47; –59]	–47 [–45; –51]	
Real-time PVI recording:	182 (31)	59 (30)	0.950
RSPV	48 (33)	18 (38)	
RIPV	40 (28)	10 (21)	
LSPV	48 (34)	16 (33)	
LIPV	41 (29)	14 (29)	
LCPV	5 (38)	1 (25)	
PV with electrical reconnection*:	100 (57)	26 (41)	0.070
RSPV	23 (52)	8 (50)	
RIPV	28 (64)	10 (62)	
LSPV	23 (55)	3 (19)	
LIPV	24 (57)	5 (31)	
LCPV	2 (100)	–	

Values are median [first quartile; third quartile], or number (%). *Reconnections of the pulmonary veins were assessed in the 60 patients who underwent repeat pulmonary vein isolation because of recurrent atrial arrhythmia. AF — atrial fibrillation; LCPV — left common pulmonary vein; LIPV — left inferior pulmonary vein; LSPV — left superior pulmonary vein; PV — pulmonary vein; PVI — pulmonary vein isolation; RIPV — right inferior pulmonary vein; RSPV — right superior pulmonary vein; SR — sinus rhythm

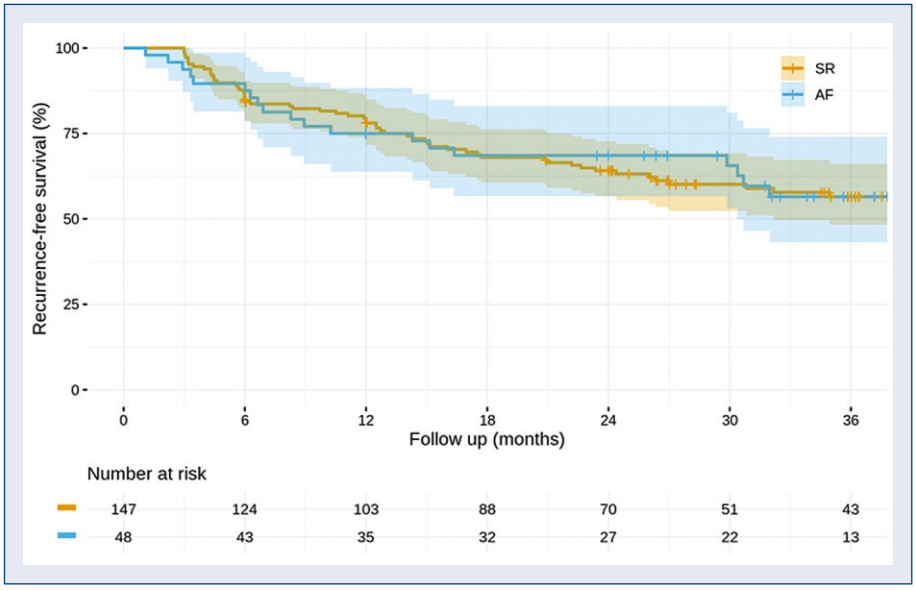

Figure 1. Freedom from atrial arrhythmia recurrence after cryoballoon ablation performed in sinus rhythm (SR; orange curve) or during atrial fibrillation (AF; blue curve). The log-rank test revealed no significant difference in arrhythmia-free survival between the groups (p = 0.8).

ergy transfer, respectively. The second-generation CB features a refrigerant injection system that provides homogeneous cooling of the entire distal hemisphere of the CB. Temperature monitoring of the CB is realized via a thermocouple located inside the balloon. Reduced atrial contractility during AF seems to enhance adherence of the CB to the atrial myocardium. As a result, the surrounding blood flow, which results in a competing warming of the balloon, is reduced. This allows for lower nadir CB temperatures and, thereby, for more effective CB applications. Accordingly, patients in the AF group appear to be at a lower risk for PV reconnection. Interestingly, data on the impact of the intraprocedural heart rhythm during point-by--point RFC ablation are inconsistent [17, 18]. It is conceivable that atrial contractility might play a greater role in "single-shot" CB ablation. During the first phase of the freeze cycle adherence of the balloon to the myocardium is essential for effective energy transfer to the tissue. The reduced atrial contractility during AF appears to support this process. Point-by-point RFC ablation is more complex and anatomic locations, e.g., the anterior or posterior aspect of the PV as well as individual anatomic variations, might pose a greater impact as compared to the relatively simple use of the CB.

Another relevant finding is that real-time recordings and proof of the occurrence of PVI is not hampered by performing CB ablation during AF. Real-time assessment of PVI is essential when applying time-to-isolation guided ablation protocols that pave the way for shorter procedure times without compromising procedural efficacy and safety [9, 19]. Aryana et al. [8] demonstrated that isolation of the PV within the first 60 s of the freeze-cycle is associated with a high durability of PVI. Therefore, the time to isolation provides one of the most powerful predictors of effective CB ablation [8].

Arrhythmia free-survival

In the current study, arrhythmia-free survival was not different between patients undergoing CB-based PVI during AF or in SR. A low nadir CB temperature is associated with a very high likelihood of durable PVI; however, our findings noted a significantly lower nadir CB temperature and a trend towards a higher durability of PVI in the AF group did not result in improved arrhythmia-free survival. The underlying causes might be multifactorial. First, a higher number of patients than provided in our analysis might be needed to demonstrate improved freedom from AF. Second, the prevalence of persistent AF was markedly higher in the AF group, and, as the experiences of previous studies have shown, results of catheter ablation for persistent AF are less successful than for paroxysmal AF [20–22]. Taking this into account, the similar arrhythmia-free survival in both groups is a positive result for the AF group.

Noteworthy, none of the 60 patients undergoing repeat ablation of AF showed permanent isolation of all PV underlining the impact of recovered PV conduction as one of the main drivers for recurrence of AF following PVI [23]. Yet, the rate of durable PVI was unexpected low at the time of repeat ablation, since previous studies reported on a proportion of patients with permanent isolation of all PV following CB ablation of 15% [6], 22% [24], and 53% [25]. However, even if these data were more convincing, durability of PVI is still not yet satisfactory. The implementation of the CB has led to greater availability of AF ablation, better reproducibility of clinical outcomes [26], and improved lesion characteristics as compared to RFC ablation [27], but the high proportion of reconnected PV demands further efforts ensuring permanent PVI following the index procedure. It also needs to be taken into consideration that only patients with symptomatic AF-recurrences were included in the study. It can be speculated that the proportion of durably isolated PVs is higher in patients without AF recurrences.

Limitations of the study

The current study is an observational, non--randomized analysis. The mode of the follow-up might have resulted in an overestimation of freedom from atrial arrhythmia recurrences. A sufficiently powered randomized comparison is mandatory before final conclusions can be drawn.

Conclusions

In this observational study, the performance of CB-based PVI during AF resulted in lower nadir CB temperatures and a trend towards higher durability of PVI when compared to procedures performed in SR. The rate of real-time PVI recording was not affected by the intraprocedural rhythm. In accordance to the present findings, in CB ablation, electrical cardioversion of AF should be performed once PVI has been obtained.

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Effect of FIXed-dose combination of ARb and statin on adherence and risk factor control: The randomized FIXAR study

Seyong Chung, Young-Guk Ko, Jung Sun Kim, Byeong-Keuk Kim, Chul-Min Ahn, Sungha Park, Sung-Jin Hong, Sang-Hak Lee, Donghoon Choi

Division of Cardiology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea

Abstract

Background: *The efficacy of fixed-dose combinations (FDCs) in improving adherence and risk factor control for cardiovascular disease has not been reported consistently. Here, we compared adherence and efficacy between an olmesartan/rosuvastatin FDC and the usual regimen.*

Methods: *In this 6-month, open-label, randomized, active-control study, we screened 154 patients; of these, 150 were randomly assigned to receive either olmesartan/rosuvastatin FDC or the usual regimen with separate angiotensin receptor blockers and statins. In total, 135 patients completed the study (median age: 68 years; male: 68.9%). The primary outcome was patients' adherence; the secondary outcomes were changes in blood pressure (BP) and lipid parameters.*

Results: *During follow-up, adherence in both groups was high and similar between the groups (98.9% and 98.3% in the FDC and usual regimen groups, respectively, p = 0.328). Changes in systolic (–8 and –5 mmHg, respectively, p = 0.084) and diastolic BP (–5 and –2 mmHg, p = 0.092) did not differ significantly, although they were numerically greater in the FDC group. Changes in low-density lipoprotein cholesterol (LDL-C) were greater in the FDC group (–13 and –4 mg/dL, respectively, p = 0.019), whereas changes in other lipid parameters were similar between the groups. The test drugs were well tolerated, showing no difference in safety between the groups.*

Conclusions: *Patients' adherence was excellent and similar in the groups, whereas the reduction in the LDL-C level was greater in the FDC group. We provide comprehensive information on the adherence and efficacy of an FDC compared to the usual regimen in Korean patients with high cardiovascular risk.*
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Key words: hypertension, hypercholesterolemia, drug therapy, renin–angiotensin system, rosuvastatin calcium

Introduction

Statins are currently the standard of care for cardiovascular prevention [1] and are commonly prescribed with antihypertensive agents for high-risk patients. The European guidelines classify patients with severe hypertension as a high-risk group, for whom active lipid-lowering therapy is recommended [2]. The American guidelines include blood pressure (BP) when calculating an individual's cardiovascular risk using a pooled cohort equation [3]. Thus, the presence of hypertension in a patient may increase the need for statin-based therapy. In the last two decades, the

Address for correspondence: Donghoon Choi, MD, PhD and Sang-Hak Lee, MD, PhD, Division of Cardiology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemun-gu, Seoul, 120-752, Korea, tel: 82-2-2228-8460, fax: 82-2-2227-7732, e-mail: cdhlyj@yuhs.ac and shl1106@yuhs.ac

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use of combination or concomitant therapies with antihypertensives and lipid-lowering agents has increased in Korea [4].

Renin–angiotensin system (RAS) blockers are recommended for patients with ischemic heart disease plus hypertension, diabetes mellitus, heart failure, or chronic kidney disease. In addition, they are recommended for patients with multi-site vascular diseases [5]. The use of RAS blockers is based on the results of studies, including the HOPE [6] and EUROPA [7] studies, which showed the benefit of RAS blockers in secondary cardiovascular prevention. In addition, considering their efficacy and safety, angiotensin receptor blockers (ARBs) and statins are frequently co-prescribed in clinical trials and real-world practice [8, 9].

Patients' adherence to a treatment regimen is known to be negatively affected by its complexity; thus, it can be improved by simplification of regimens [10]. Previous studies compared a fixed-dose combination (FDC) of acetylsalicylic acid, a statin, and an angiotensin-converting enzyme inhibitor (ACEI) with a regimen of individual drugs. Several studies reported that an FDC can be helpful in increasing patients' adherence [11–13]. Furthermore, a recent study in low- and middle-income countries found that an FDC is cost-effective in secondary cardiovascular disease prevention [14]. Conversely, the UMPIRE study demonstrated that an FDC was effective in controlling BP and low-density lipoprotein cholesterol (LDL-C) level [11]. However, several studies found no differential effect of FDCs and usual regimens in terms of control of risk factors [12, 13, 15]. Moreover, data on the effects of FDCs in East Asian patients are extremely limited.

Considering these results, the current FIXAR study aimed to compare the adherence of two groups of patients receiving an FDC consisting of olmesartan and rosuvastatin or the usual regimen. The usual regimen included individual drugs of any ARBs and statins that have comparable efficacy with that of the FDC. Secondly, we compared changes in BP and lipid parameters, including the LDL-C level. Drug tolerability in the study population was also assessed.

Methods

Study participants

Men and women aged 20–80 years who required antihypertensive and lipid-lowering therapies were eligible for the study. Patients already under pharmacological treatment for hypertension and high blood cholesterol were initially screened. The need for pharmacological treatment was determined based on the guidelines of the 2013 Korean Society of Hypertension [16] and the Korean Society of Lipid and Atherosclerosis [17]. Briefly, the inclusion criteria were as follows: patients with BP ≥ 140/90 mmHg or patients already under antihypertensive treatment. Furthermore, the patients had one of the following conditions: 1) atherosclerotic cardiovascular disease; 2) diabetes, carotid artery stenosis with ≥ 50% luminal narrowing, or aortic aneurysm and LDL-C level ≥ 100 mg/dL; 3) two or more cardiovascular risk factors and LDL-C level ≥ 130 mg/dL; or 4) no risk factors or one risk factor and LDL-C level ≥ 160 mg/dL. The exclusion criteria were patients 1) with uncontrolled hypertension (systolic BP ≥ 180 mmHg or diastolic BP ≥ 110 mmHg); 2) with uncontrolled diabetes mellitus (hemoglobin A1c ≥ 9% or fasting blood glucose ≥ 160 mg/dL); 3) with high-grade heart failure or clinically significant arrhythmia or who experienced cardiovascular or cerebrovascular events within 3 months of screening; and 4) with a history of chronic liver disease, chronic kidney disease (glomerular filtration rate < 60 mL/min/1.73 m^2), or systemic inflammatory disease or those receiving systemic anti-inflammatory treatment; 5) with additional lipid-lowering agents other than the study drugs; as well as 6) pregnant or breast-feeding women or women with child-bearing potential not receiving contraception. All participants provided written informed consent.

Study design

This was a 6-month, open-label, randomized, active-control study (ClinicalTrials.gov ID: NCT04061824). The institutional review board of Severance Hospital, Seoul, Korea approved the protocol (No. 4-2015-1122). At the screening visit, patients were interviewed regarding their medical history, and they underwent a physical examination and laboratory assessment. Participants who met the inclusion criteria were randomly assigned in a 1:1 ratio to receive one of the following two regimens: 1) an FDC of olmesartan/rosuvastatin (20 mg/5 mg, 20 mg/10 mg, 20 mg/20 mg, or 40 mg/20 mg); or 2) the usual regimen with ARBs and statins. The drug doses given to the participants of the FDC group were determined according to the potency of the ARBs and statins previously received by the participants (i.e. before enrollment). After randomization, the participants were followed up at the end of the 3rd and 6th months for outcome evaluation. Although other medications, including

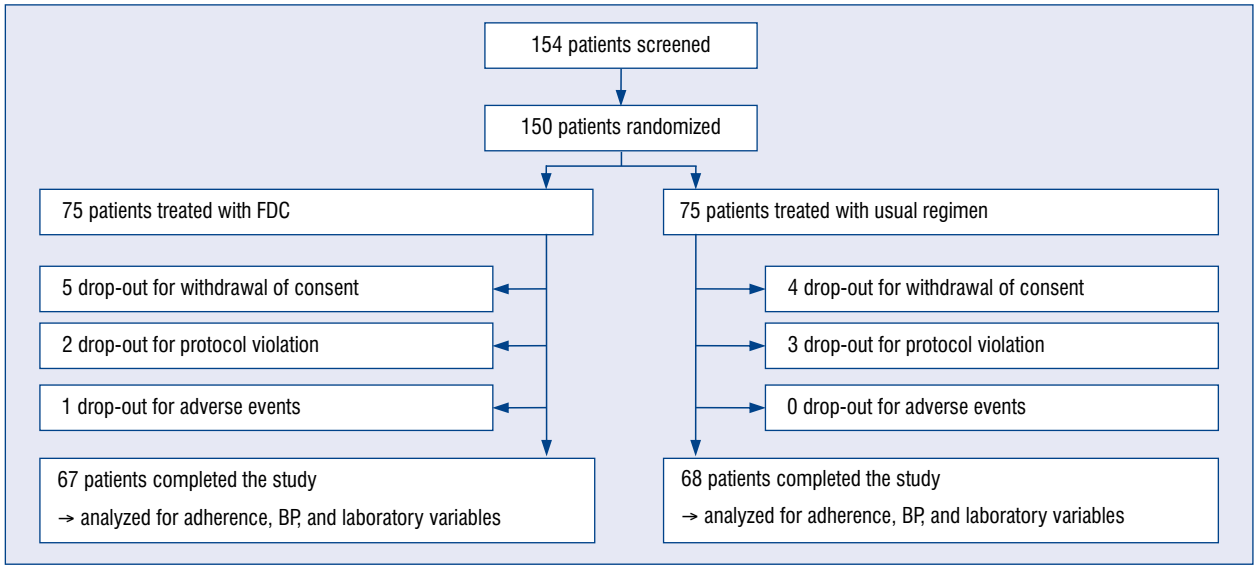

Figure 1. Study profile showing the numbers of patients who participated or dropped out; BP — blood pressure; FDC — fixed-dose combination.

antiplatelet, anti-hypertensive, or anti-diabetic agents, were allowed in both groups, patients who changed drugs or doses during the study period were excluded from analysis.

Adherence was estimated by direct measurement via pill count. Patients were instructed to return all surplus medications at the follow-up visits. Adherence (%) was calculated as: the number of pills dispended/the number of pills prescribed × 100. In addition, BP was measured, and fasting blood samples were collected at randomization and at the end of the 6th month. BP was measured by the same person at a regular time using a validated electronic sphygmomanometer (HEM-7080 IT; Omron Healthcare, Kyoto, Japan). Laboratory parameters, including lipid profiles, were measured at these time points. Samples were analyzed within 4 h of collection by a local laboratory certified by the Korean Society of Laboratory Medicine. Tolerability was assessed from adverse event reports, history taking, physical examinations, and laboratory evaluations.

Statistical analysis

The primary outcome was drug adherence during the study period. The secondary outcomes included changes in systolic and diastolic BP as well as total cholesterol, triglyceride, high-density lipoprotein-cholesterol (HDL-C), and LDL-C levels. A minimum of 62 participants per treatment group were required, assuming a power of 0.80, to determine the superiority of the FDC to the usual regimen in terms of the primary outcome. A 5 ± 10% difference in adherence between the groups was defined as significant. Assuming a 10% dropout rate, at least 68 individuals per group were recruited. The primary and secondary outcomes were analyzed in the population that underwent follow-up. Tolerability was assessed in all patients who were administered the study agents more than once. Differences in categorical variables between the groups were examined using the χ^2 test, whereas those in continuous variables were assessed using Student's t-test. The paired t-test was used to evaluate differences before and after treatment in each group. Differences were considered significant at p values < 0.05 (two-sided). All data were analyzed using SAS software 9.3 (SAS Korea, Seoul, Korea)

Results

Baseline characteristics

In total, 154 patients were screened; of these, 150 were subsequently randomized (Fig. 1). At screening, 4 patients did not meet the inclusion criteria and were excluded. Of the 150 randomized participants, 135 completed the study, whereas 15 patients dropped out for the following reasons: 9 due withdrawal of consent, 5 due to protocol violation, and 1 due to adverse events. The clinical characteristics of the patients are shown in Table 1. The median age was 68 years, and 93 (68.9%)

Table 1. Clinical characteristics of the study participants.

	FDC (n=67)	Usual regimen (n = 68)	P
Age [years]	68 (59, 73)	68 (60, 72)	0.923
Male	46 (68.6%)	47 (69.1%)	0.954
Medical history:			
Hypertension	67 (100%)	68 (100%)	1.000
Diabetes mellitus	22 (32.8%)	18 (26.4%)	0.418
Hypercholesterolemia	62 (92.5%)	61 (89.7%)	0.563
Coronary artery disease	41 (61.1%)	42 (61.7%)	0.946
Peripheral artery disease	5 (7.4%)	3 (4.4%)	0.453
Body mass index [kg/m^2]	24.8 (23.7, 26.8)	24.7 (23.3, 26.9)	0.956
Systolic BP [mmHg]	129 (119, 140)	129 (116, 140)	0.606
Diastolic BP [mmHg]	77 (69, 85)	75 (68, 84)	0.865
Lipid profile [mg/dL]:			
Total cholesterol	153 (136, 168)	151 (128, 177)	0.904
Triglyceride	117 (91, 149)	114 (86, 171)	0.979
HDL-C	47 (40, 55)	47 (40, 56)	0.760
LDL-C	79 (65, 90)	76 (61, 98)	0.604

Data are presented as median (interquartile range) or number (%); FDC — fixed-dose combination; BP — blood pressure; HDL-C — high--density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol

patients were male. Forty (29.6%) patients had diabetes mellitus, and 83 (61.5%) had a history of coronary artery disease. The median systolic BP was 129 mmHg, and the LDL-C level was 78 mg/dL at randomization. Demographic variables did not differ significantly between the groups. The doses of olmesartan and rosuvastatin used in the FDC group and ARBs and statins in the usual regimen group are shown in Table 2.

Primary and secondary outcomes

At the 6-month follow-up, patients' adherence to the regimens was not significantly different between the two groups (98.9% and 98.3% in the FDC and usual regimen groups, respectively, p = 0.328). The median change in systolic BP did not differ significantly between the two groups, although it was numerically greater in the FDC group than in the usual regimen group (–8 mmHg and –5 mmHg, respectively, p = 0.084). Similarly, the change in diastolic BP was similar in the two groups (–5 mmHg and –2 mmHg, respectively, p = 0.092). However, the median change in the LDL-C level was greater in the FDC group than in the usual regimen group (–13 mg/dL and –4 mg/dL, respectively, p = 0.019). The changes in the other lipid parameters were not different between the two groups (Table 3).

Tolerability

The proportion of patients with adverse events in the FDC and usual regimen groups was similar (21 [31.3%] and 18 [26.4%] patients, respectively, p = 0.573). The test drugs were well tolerated during the study, and the number of patients with serious adverse events was not different between the groups (3 [4.4%] in both groups, p = 1.000). The relatively common adverse events observed in the study population included dizziness, upper gastrointestinal symptoms, upper respiratory tract infection symptoms, headache, and myalgia, in order of frequency (Table 4).

Discussion

The major findings of our study included the following: 1) Patients' adherence was higher than 98% in the FDC and usual regimen groups and did not differ between the two groups. 2) The changes in systolic and diastolic BP were not significantly different between the two groups, although they were numerically greater in the FDC group. 3) The LDL-C level was reduced to a greater extent in the FDC group than in the usual regimen group. 4) Tolerability of the study regimens in the two groups was similar during the study. Our study provides comprehensive information comparing

Table 2. Doses of angiotensin receptor blockers (ARBs) and statins used in patients in the fixed-dose combination (FDC) and usual regimen groups, who completed the study.

FDC	Number of patients (n = 67)	Usual regimen	Number of patients (n = 68)
Olmesartan 20 mg/ /rosuvastatin 5 mg	12 (17.9)	Equivalent regimens:	13 (19.1)
		Candesartan 8 mg and atorvastatin 10 mg	3
		Candesartan 8 mg and pravastatin 40 mg	1
		Candesartan 8 mg and simvastatin 20 mg	1
		Fimasartan 60 mg and pitavastatin 2 mg	1
		Olmesartan 20 mg and atorvastatin 10 mg	1
		Olmesartan 20 mg and rosuvastatin 5 mg	2
		Telmisartan 40 mg and rosuvastatin 5 mg	2
		Valsartan 80 mg and pitavastatin 2 mg	1
		Valsartan 80 mg and pravastatin 40 mg	1
Olmesartan 20 mg/ /rosuvastatin 10 mg	25 (37.3)	Equivalent regimens:	26 (38.2)
		Candesartan 8 mg and rosuvastatin 10 mg	6
		Fimasartan 30 mg and rosuvastatin 10 mg	1
		Fimasartan 30 mg and simvastatin 40 mg	1
		Losartan 50 mg and fluvastatin 80 mg	1
		Olmesartan 20 mg and rosuvastatin 10 mg	9
		Telmisartan 40 mg and rosuvastatin 10 mg	3
		Valsartan 80 mg and pitavastatin 4 mg	1
		Valsartan 80 mg and rosuvastatin 10 mg	3
		Valsartan 80 mg and atorvastatin 20 mg	1
Olmesartan 20 mg/ /rosuvastatin 20 mg	19 (28.4)	Equivalent regimens:	20 (29.4)
		Candesartan 8 mg and atorvastatin 40 mg	1
		Candesartan 8 mg and rosuvastatin 20 mg	1
		Losartan 50 mg and atorvastatin 40 mg	1
		Olmesartan 20 mg and rosuvastatin 20 mg	4
		Telmisartan 40 mg and atorvastatin 40 mg	1
		Telmisartan 40 mg and rosuvastatin 20 mg	2
		Valsartan 80 mg and atorvastatin 40 mg	1
		Valsartan 80 mg and rosuvastatin 20 mg	9
Olmesartan 40 mg/ /rosuvastatin 20 mg	11 (16.4)	Equivalent regimens:	9 (13.2)
		Candesartan 16 mg and rosuvastatin 20 mg	1
		Losartan 100 mg and rosuvastatin 20 mg	1
		Olmesartan 40 mg and rosuvastatin 20 mg	3
		Telmisartan 80 mg and atorvastatin 40 mg	1
		Valsartan 160 mg and atorvastatin 40 mg	1
		Valsartan 160 mg and rosuvastatin 20 mg	2

Data are presented as number (%)

the usual regimen and an FDC comprising an ARB and a statin in Korean patients with high cardiovascular risk.

We found that patients' adherence to the study regimens, including ARBs and statins, as well as the FDC, was higher than that in most previous studies. In a meta-analysis of 5 prior studies, the adherence rates were 93.0% and 92.8% in the FDC and control groups, respectively [18]. Similarly, a meta-analysis of 9 studies by Huffman et al. [19] reported a 15-month adherence of 86% and 65% for the FDC and control groups, respectively. Con-

Table 3. Other anti-hypertensive agents used in patients in the fixed-dose combination (FDC) and usual regimen groups, who completed the study.

Regimen	FDC (n = 67)	Usual regimen (n = 68)
Beta-blocker	18 (26.9%)	22 (32.4%)
CCB	17 (25.4%)	14 (20.6%)
Diuretics	2 (3.0%)	2 (2.9%)
Beta-blocker and CCB	3 (4.5%)	5 (7.4%)
Beta-blocker and diuretics	0 (0%)	2 (2.9%)
CCB and diuretics	1 (1.5%)	1 (1.5%)
Beta-blocker, CCB, and diuretics	2 (3.0%)	1 (1.5%)
Others	1 (1.5%)	0 (0%)

Data are presented as number (%); CCB — calcium channel blocker

Table 4. Primary and secondary outcome variables.

	FDC (n = 69)	Usual regimen (n = 73)	P
Primary outcome variables:			
Adherence [%]	98.9 (96.1, 100.0)	98.3 (95.6, 100.0)	0.328
Secondary outcome variables:			
Systolic BP [mmHg]	–8 (–18, 1)	–5 (–15, 9)	0.084
Diastolic BP [mmHg]	–5 (–12, 2)	–2 (–10, 6)	0.092
Total cholesterol [mg/dL]	–11 (–27, 1)	–5 (–21, 8)	0.195
Triglyceride [mg/dL]	6 (–32, 37)	0 (–29, 21)	0.193
HDL-C [mg/dL]	1 (–4, 5)	1 (–5, 5)	0.878
LDL-C [mg/dL]	–13 (–25, –1)	–4 (–16, 7)	0.019

Data are presented as median (interquartile range); FDC — fixed-dose combination; BP — blood pressure; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol

Table 5. Adverse events.

	FDC (n = 75)	Usual regimen (n = 75)	P
Patients with adverse events	21 (31.3%)	18 (26.4%)	0.573
Patients with serious adverse events	3 (4.4%)	3 (4.4%)	1.000
Frequency of each adverse event:			
Dizziness	8	2	
Upper GI symptoms	6	4	
URI symptoms	4	5	
Headache	4	3	
Myalgia	5	1	
Edema	2	2	
Skin problems	1	2	
Minor bleeding	0	3	
Others	9	15	

Data are presented as number (%); FDC — fixed-dose combination; GI — gastrointestinal; URI — upper respiratory tract infection

versely, a recent study conducted in Iran revealed that the adherence to an FDC consisting of acetylsalicylic acid, a statin, and an ACEI or hydrochlorothiazide was 80.5% [20]. A study by Selak et al. [12] showed that the 12-month adherence to an FDC including acetylsalicylic acid, statin, and an ACEI was 81%, whereas that to the usual regimen was 46%. In addition, the 15-month adherence was 86% and 65% in users of the FDC and usual regimen, respectively, in the UMPIRE study [11]. In the Kanyini GAP study, the 18-month adherence was 70% and 47% in the FDC and control groups, respectively [13]. Patients' adherence to regimens can be affected by the follow-up duration [21], patient's age [22], underlying disease, number of drugs [22], and adverse events associated with the drugs. A meta-analysis by Webster et al. [21] revealed that adherence to a polypill was higher at earlier follow-up time points than at later follow-up time points. The adherence in our study was higher than that in other studies, and it may be related to the short follow-up duration and relatively advanced age of the participants. Furthermore, we used ARBs as antihypertensive agents; thus, the higher safety profile of ARBs than that of ACEIs might have influenced patients' adherence. Although the reason for the high adherence rate in the usual regimen group in our study is not completely understood, it might be associated with the factors mentioned above.

In our study, the changes in the LDL-C level were greater in the FDC group than in the usual regimen group. A recent meta-analysis reported that achievement rates of BP and LDL-C level targets were higher in patients receiving a polypill than in those receiving the usual regimens [23]. In other studies, the reduction in BP and LDL-C level was also greater among FDC users [11]. In particular, patients who were undertreated or exhibited poor adherence at the baseline obtained greater benefit from FDCs [21, 24]. However, as mentioned in the introduction, FDCs or the usual regimen did not show significant differences in controlling the risk factors in many studies [12, 13]. It is not clear why, in our study, the LDL-C level was reduced to a greater extent in the FDC group than in the usual regimen group, despite similar adherence in the two groups. We permitted the use of diverse statins in the usual regimen group, whereas only rosuvastatin was used in the FDC group. Therefore, differences in individual responses to diverse statins in the usual regimen group might have partially caused the differential results. For example, statins such as atorvastatin 20 mg and simvastatin 40 mg are considered to have lipid-lowering efficacy similar to that of rosuvastatin 10 mg. However, these regimens have been found to elicit slightly greater LDL-C reductions in some studies [25, 26]. Therefore, this modestly higher effect of rosuvastatin, compared to other statins with similar efficacy, might have induced greater LDL-C reduction in the patients receiving FDC of olmesartan/rosuvastatin in this study. However, further investigation is needed to fully explain this finding.

In the current study, the rates of patients experiencing adverse events were not different between the two groups, although it was numerically higher in the FDC group than in the other group. In an analysis of 9 prior studies, this rate was higher in the FDC group (30% and 24% in the FDC and usual regimen groups, respectively) [19]. These rates are consistent with those in our study. In addition, a study analyzing 9 randomized controlled trials revealed a modestly higher rate of adverse events in the FDC group [27]. However, the differential safety profile between FDCs and the usual regimen was not consistent in these previous studies. A meta-analysis involving 5 studies identified no significant difference in the rates of adverse events between the FDC and usual regimen groups [18].

Limitations of the study

Our study had some limitations. First, we did not fully assess concomitantly administered pharmacological agents. Because a large proportion of the study population had coronary or peripheral artery disease, they might have received additional drugs, such as antiplatelet agents. Concomitant administration of additional drugs might have reduced the single-pill effect in the FDC group. Second, our study was conducted in a tertiary hospital, and most participants were well-treated at baseline. Thus, the adherence in the two groups was high, and the inter-group difference might have been minimized. Third, the follow-up duration was 6 months, which is shorter than those in previous studies. This might have attenuated any potential difference in the primary and secondary outcomes between the two groups. Finally, our study was open label. Despite our best attempts to prevent it, potential bias caused by the study design cannot be completely ruled out. Nevertheless, it is noteworthy that the current study was well performed to investigate our original study objective, and, for the first time, to our knowledge, we showed comparison data of the efficacy of an FDC and the usual regimen of hypertension in Korean patients with multiple risk factors.

Conclusions

In conclusion, patients' adherence to the test regimens was excellent and similar in the two groups. The LDL-C level was reduced to a greater extent in the FDC group than in the usual regimen group, whereas changes in BP and other lipid parameters did not differ between the groups. Our study provides comprehensive information on the efficacy of an FDC compared with that of the usual regimen in Korean patients with high cardiovascular risk.

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Conflict of interest: None declared

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Systemic inflammation and oxidative stress contribute to acute kidney injury after transcatheter aortic valve implantation

Arunraj Navaratnarajah[1, 2], Amit Bhan[2], Emma Alcock[3], Tracy Dew[2], Mark Monaghan[2], Ajay M. Shah[2], Olaf Wendler[4], Philip MacCarthy[2], Rafal Dworakowski[2, 5]

[1]Renal Section, Department of Medicine, Hammersmith Hospital Campus, Imperial College London, United Kingdom
[2]Department of Cardiology, King's College Hospital and King's College London, British Heart Foundation Centre, London, United Kingdom
[3]Department of Anaesthesia, King's College Hospital and King's College London, British Heart Foundation Centre, London, United Kingdom
[4]Department of Cardiothoracic Surgery, King's College Hospital and King's College London, British Heart Foundation Centre, London, United Kingdom
[5]Department of Cardiology, Medical University of Gdansk, Poland

Abstract

Background: *Acute kidney injury (AKI) is a frequent complication of transcatheter aortic valve implantation (TAVI) and has been linked to preexisting comorbidities, peri-procedural hypotension, and systemic inflammation. The extent of systemic inflammation after TAVI is not fully understood. Our aim was to characterize the inflammatory response after TAVI and evaluate its contribution to the mechanism of post-procedural AKI.*

Methods: *One hundred and five consecutive patients undergoing TAVI at our institution were included. We analyzed the peri-procedural inflammatory and oxidative stress responses by measuring a range of biomarkers (including C-reactive protein [hsCRP], cytokine levels, and myeloperoxidase [MPO]), before TAVI and 6, 24, and 48 hours post-procedure. We correlated this with changes in renal function and patient and procedural characteristics.*

Results: *We observed a significant increase in plasma levels of pro-inflammatory cytokines (hsCRP, interleukin 6, tumor necrosis factor alpha receptors) and markers of oxidative stress (MPO) after TAVI. The inflammatory response was significantly greater after transapical (TA) TAVI compared to transfemoral (TF). This was associated with a higher incidence of AKI in the TA cohort compared to TF (44% vs. 8%, respectively, $p < 0.0001$). The incidence of AKI was significantly lower when N-acetylcysteine (NAC) was given peri-procedurally (12% vs. 38%, $p < 0.005$). In multivariate analysis, only the TA approach and no use of NAC before the procedure were independent predictors of AKI.*

Conclusions: *TAVI creates a significant post-procedural inflammatory response, more so with the TA approach. Mechanisms of AKI after TAVI are complex. Inflammatory response, hypoperfusion, and oxidative stress may all play a part and are potential therapeutic targets to reduce/prevent AKI.* (Cardiol J 2022; 29, 5: 824–835)

Key words: severe aortic stenosis, transcatheter aortic valve implantation, acute kidney injury, systemic inflammation

Address for correspondence: Dr. Rafal Dworakowski, MD, PhD, Consultant Cardiologist, King's College Hospital, Cardiovascular Division, Hambledon Wing, Denmark Hill, London, SE5 9RS, United Kingdom, tel: +44-(0)203 299 1308, fax: +44-(0)203 299 3489, e-mail: rdworakowski@nhs.net

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Introduction

Acute kidney injury (AKI) is a recognized complication of conventional valve surgery using cardiopulmonary bypass and is associated with poor outcomes [1]. Aside from preexisting comorbidities, important contributors include hypotension during cardiopulmonary bypass and post-operative systemic inflammation. TAVI does not require cardiopulmonary bypass, but post-procedural AKI frequently occurs, in 19% to 33% of patients [2, 3]. Although the prevalence of chronic kidney disease in transcatheter aortic valve implantation (TAVI) patients is higher than in surgical cohorts (because of their greater age and higher overall risk), the exact mechanism of AKI following TAVI is unclear. In some studies, AKI has been linked with the volume of intra-operative contrast agent used [4], but other factors have also been identified including blood transfusions [5].

Little is known about the magnitude of the inflammatory response, oxidative stress, and myocardial/renal injury after TAVI. Systemic inflammatory response syndrome (SIRS) after TAVI, measured using C-reactive protein (CRP) and body temperature, is an independent predictor of mortality [6]. The precise etiology of SIRS in this setting is unclear but may in part relate to myocardial damage and pump failure. It is clear that myocardial damage is a poor prognosticator, and Yong et al. [7] have shown recently that a peri-procedural increase in markers of myocardial injury independently predicts a poor outcome at 30 days after TAVI. Inflammatory markers such as interleukin 6 (IL-6) [8] and tumor necrosis factor alpha (TNFα) [9] have been correlated with AKI after coronary artery bypass grafting, and although likely to be relevant, they have not previously been demonstrated in a TAVI population.

The aim of our study was to analyze and clarify the systemic inflammatory response, the change in oxidative stress, and magnitude of myocardial injury after TAVI and thereafter to explore associations with AKI and procedural outcome.

Methods

Patient population

We prospectively included 105 consecutive patients with severe aortic stenosis, who underwent TAVI either via a transfemoral (TF TAVI, n = 60) or a transapical approach (TA TAVI, n = 45) using Edwards-Sapien and Sapien XT transcatheter heart valves (Edwards Lifesciences, Inc., CA, USA) between July 2009 and July 2012. The study was approved by the local research Ethics Committee. All subjects provided written informed consent.

Mortality tracking was undertaken by the National Health Service Central Register using unique patient identifiers for all patients enrolled in this study.

The primary endpoint of the study was the occurrence of AKI. We utilized the Acute Kidney Injury Network classification of AKI [10]. Clinical outcome and complications were recorded using Valve Academic Research Consortium-2 definitions [11]. The estimated glomerular filtration rate was calculated by the simplified Modification of Diet in Renal Disease formula.

Systemic inflammatory response syndrome was defined as fulfilling at least two of the following criteria during the first 48 h after TAVI: temperature < 36.0°C or > 38.0°C, heart rate > 90 bpm, and leucocyte count > 12 or < 4 (10^9/L).

Preoperative protocol to prevent AKI

N-acetylcysteine (NAC) was given at the physician's discretion 1 day pre-TAVI at 600 mg bd and continued for 48 h post TAVI in 53% of patients (n = 60).

TAVI procedure and anesthesia

Transfemoral TAVI was performed using the conventional technique [12]. A similar general anesthetic technique was used in all cases regardless of access site. Surgical exposure of the femoral artery was used as the mode of arterial access in TF patients. Initial fluid replacement was with 1000 mL compound sodium lactate. Blood pressure was maintained (systolic > 100 mmHg) during the procedure with metaraminol boluses (50–100 μg). No patient required catecholamine infusion post-procedure.

Invasive cardiac output monitoring

The FloTrac system uses a clinically validated algorithm to provide continuous cardiac output, stroke volume, and systemic vascular resistance measurements. Heart rate, and systolic and diastolic blood pressure were recorded at each time point. A Vigileo™ (Edwards Lifesciences, Irvine, CA, USA) monitor with software version 1.01 was connected to the radial artery catheter via a FloTrac™ (Edwards Lifesciences, Irvine, CA, USA) pressure sensor.

Biomarkers

Blood samples were obtained pre-TAVI and 4–6 h, 22–26 h, and 44–52 h post-procedure from

a central line. Intervals for sampling were based on data from Sinning et al. [13], in which an elevated leucocyte count and IL-6 was already observed 4 h after TAVI and reached a peak level at 48 h after TAVI. Serum was isolated within 1 h of collection and samples stored at –80°C until thawed for determination of biomarkers, which were measured as follows:

Markers of inflammation and oxidative stress. Serum hsCRP was measured using a latex-enhanced immunoturbidimetric assay (PZ Corman, Lublin, Poland). The precision of the assays is expressed as the between-run coefficient of variation (%CV). The %CV of the hsCRP assay for concentrations of 0.047, 0.218, and 0.976 mg/L was 6.97, 3.34, and 1.23%, respectively.

Tumor necrosis factor alpha, tumor necrosis factor alpha receptor 1 (TNFαR1), tumor necrosis factor alpha receptor 2 (TNFαR2), and IL-6 were measured using a Luminex® Bead-based Multiplex Assay system.

Serum myeloperoxidase (MPO) was measured using the quantitative sandwich enzyme-linked immunoassay (ELISA) technique (R&D Systems Europe Ltd., United Kingdom). The %CV of the MPO assay for concentrations of 15.7, 32.4, and 64.1 ng/mL was 7.5%, 7.7%, and 6.6%, respectively.

Markers of renal injury. Plasma neutrophil gelatinase-associated lipocalin (NGAL) was measured using a sandwich ELISA with wells coated with a monoclonal antibody against NGAL (BioPorto Diagnostics A/S, Denmark). The %CV of the NGAL assay for concentrations 1.2–4 pg/mL was 3%.

The assay is linear up to 1000 pg/mL.

Serum cystatin C was measured using a latex-enhanced immunoturbidimetric assay (Siemens Healthcare Diagnostics Ltd., UK). The lowest concentration that can be distinguished from zero is 0.1 mg/L.

Markers of myocardial injury. Serum creatine kinase MB (CK-MB) was measured using the Immulite 2000 assay (a chemiluminescent enzyme-labeled immunometric assay, reagent from Siemens Healthcare Diagnostics, Ltd., UK). The %CV of the CK-MB assay for concentrations of 13.9, 54.3, and 95.4 ng/mL was 5.8%, 5.5%, and 6.1%, respectively.

Markers of heart failure and neurohormonal activation. N-terminal pro-B-type natriuretic peptide (NT-proBNP) was measured on a Siemens Immulite 2000 analyzer (a two-site chemiluminescence immunoassay). The %CV of the BNP assay for concentrations of 35.6, 1430, and 29,725 pg/mL was 5.4%, 3%, and 4.1%, respectively.

Receptor for interleukin-33 (ST2) (R&D Systems Europe, Ltd., UK) was measured with a quantitative sandwich enzyme immunoassay technique. The %CV of the ST2 assay for concentrations of 273, 628, and 1027 pg/mL was 5.6%, 4.4%, and 4.5%, respectively.

Aldosterone (Siemens Medical Solutions Diagnostics, 5700 West 96th Street, LA, CA 90045-5597, USA) was measured with a solid-phase radioimmunoassay, based on aldosterone-specific antibody immobilized to the wall of a polypropylene tube. The %CV of the aldosterone assay for concentrations of 65, 448, and 813 pg/mL was 3.5%, 15.3%, and 19%, respectively.

Statistical analysis

Data are presented as mean ± standard deviation and ± SEM when appropriate. Categorical variables are given as frequencies and percentages. The Fisher exact test was used to compare categorical variables in different groups. Continuous variables were tested for normality with the Shapiro-Wilk test. For continuous variables, Student's t-test or Kruskal-Wallis test, as appropriate, was performed for comparison between two groups. Two-way repeat measures ANOVA followed by Tukey post hoc test was used to compare groups at multiple time points. Variables with evidence of heterogeneity of variance were analyzed with nonparametric tests.

Logistic regression modeling was used to assess the short-term outcome and to determine independent predictors of AKI. In a multivariate regression analysis, we adjusted for significant predictors of 12-month mortality in the univariate analysis. Survival curves according to the occurrence of AKI were plotted by the Kaplan-Meier method and compared using the Wilcoxon test. We employed a univariate Cox proportional hazard model to examine the association of AKI and other clinical characteristics with cumulative 12-month mortality and to evaluate the impact on long-term clinical outcome. $P < 0.05$ was considered to be statistically significant.

Analyses were performed using the JMP 9 statistical package (SAS, USA).

Results

Pre-procedural patient characteristics

Baseline patient characteristics and use of pre-procedural medications with potential effect on post-operative kidney function are summarized in Table 1. AKI was associated with peripheral vascu-

Table 1. Pre-procedural patient characteristics and medications according to the occurrence of acute kidney injury (AKI).

	All patients (n = 105)	No AKI (n = 81)	AKI (n = 24)	P
Pre-procedural patient characteristics				
Age [years]	84 ± 6	84 ± 6	83 ± 5	0.8
Male gender	50 (48%)	38 (47%)	12 (50%)	0.8
logistic EuroSCORE [%]	23 ± 11	22 ± 10	26 ± 12	0.2
Coronary artery disease	51 (49%)	39 (48%)	12 (50%)	0.5
Peripheral vascular disease	18 (17%)	9 (11%)	9 (38%)	< 0.005
Previous MI	13 (12%)	8 (10%)	5 (20%)	0.2
Previous cardiac surgery	22 (21%)	15 (19%)	7 (29%)	0.3
Previous PCI	19 (18%)	12 (15%)	7 (29%)	0.1
Previous stroke/TIA	15 (15%)	9 (11%)	6 (25%)	0.1
Chronic obstructive pulmonary disease	32 (31%)	27 (33%)	5 (21%)	0.23
Pulmonary hypertension (> 60 mmHg)	16 (15%)	11 (13%)	5 (21%)	0.7
Diabetes	25 (24%)	17 (21%)	8 (33%)	0.2
Baseline hemoglobin [g/dL]	12.4 ± 1.6	12.5 ± 0.2	11.8 ± 0.3	0.2
Creatinine [μmol/L]	94 ± 28	91 ± 3	105 ± 6	< 0.05
eGFR [mL/min/1.73 m^2]	61 ± 16	63 ± 2	56 ± 3	0.05
LVEF [%]	53 ± 12	53 ± 1	53 ± 3	0.93
AVA [cm^2]	0.68 ± 0.18	0.69 ± 0.02	0.69 ± 0.02	0.8
Peak pressure gradient [mmHg]	80 ± 25	83 ± 3	77 ± 5	0.3
Mean pressure gradient [mmHg]	46 ± 16	48 ± 2	42 ± 3	0.1
Left ventricle mass [g]	171 ± 51	171 ± 6	167 ± 11	0.5
Cystatin C [mg/L]	1.09 ± 0.51	1.04 ± 0.33	1.13 ± 0.37	0.3
NT-proBNP [pg/mL]	4618 ± 5934	4513 ± 752	4962 ± 908	0.8
NGAL [μg/L]	116.4 ± 65.0	108.8 ± 6.5	141.3 ± 18.4	< 0.05
Pre-procedural medications				
Pre-procedural NAC	60 (57%)	53 (65%)	7 (29%)	< 0.005
Thiazides	9 (9%)	5 (6%)	4 (17%)	0.2
NSAIDs	60 (58%)	46 (58%)	14 (58%)	1.0
Loop diuretics	61 (59%)	47 (59%)	14 (58%)	1.0
ACEI/ARB	45 (44%)	34 (43%)	11 (46%)	0.8

MI — myocardial infarction; PCI — percutaneous coronary intervention; TIA — transient ischemic attack; eGFR — estimated glomerular filtration rate; LVEF — left ventricular ejection fraction; AVA — aortic valve area; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NGAL — neutrophil gelatinase-associated lipocalin; NAC — N-acetylcysteine; NSAIDs — non-steroidal anti-inflammatory drugs; ACEI — angiotensin converting enzyme inhibitors; ARB — angiotensin II receptor blockers

lar disease, higher pre-procedural creatinine, lower transvalvular gradients, and higher N-GAL levels. Only 29% of patients subsequently developing AKI had received NAC compared to 65% of those who did not develop AKI ($p < 0.005$). Forty-seven per cent (n = 21) of patients undergoing TA TAVI and 65% (n = 39) undergoing TF TAVI received NAC. There was a higher rate (RR 5.7; 1.6–25.1, $p < 0.05$) of AKI in patients who did not receive NAC (38% vs. 12%, $p < 0.005$). This difference was significant in the TF group (19% vs. 3%, $p < 0.05$) but not in the TA group (54% vs. 29%, $p = 0.08$).

Procedural outcome and predictors of post-TAVI AKI

The valve prosthesis was successfully deployed in all patients (100%) with no peri-procedural deaths (0%) and no conversion to open surgery (0%). The combined early safety endpoint at 30 days was 31% (n = 33).

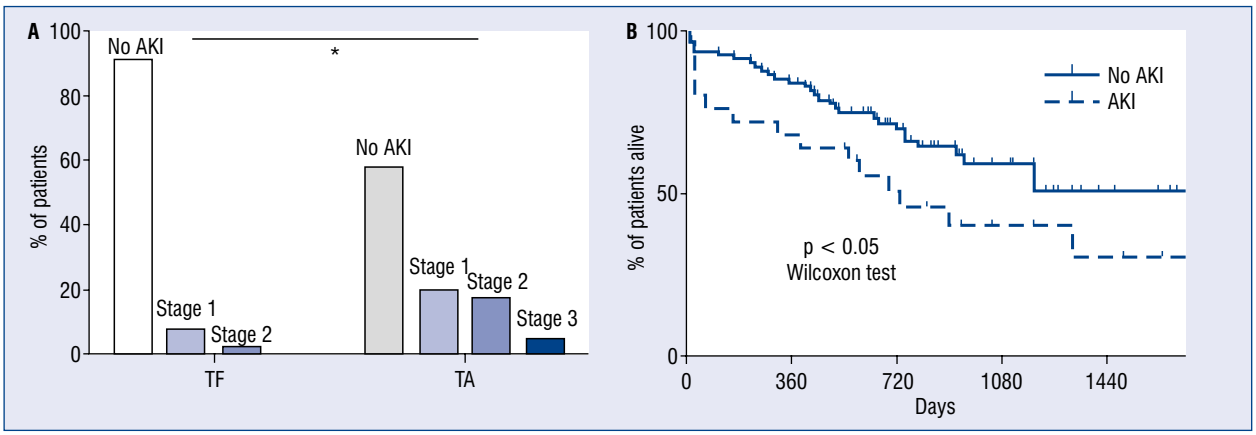

Figure 1. A. Incidence of acute kidney injury (AKI) according to access site (transfemoral [TF] vs. transapical [TA]). There was a significantly higher frequency of AKI in the transapical group (chi-square test, $p < 0.005$); **B.** Kaplan-Meier curves for patient with AKI and with no post-procedural AKI (Wilcoxon test, $p < 0.05$). There was higher mortality in the group developing AKI; *$p < 0.005$.

Table 2. Procedural characteristics and post-procedural complications (as defined by the Valve Academic Research Consortium-2) according to the occurrence of acute kidney injury (AKI)

	All patients (n = 105)	No AKI (n = 81)	AKI (n = 24)	P
Procedural characteristics				
Route transapical	45 (43%)	26 (35%)	19 (79%)	< 0.001
Valve size 23/26/29 mm	55/41/9	47/28/6	8/13/3	0.1
Volume of contrast [mL]	119 ± 52	117 ± 5	125 ± 13	0.6
Blood transfusion required	39 (37%)	28 (35%)	11 (46%)	0.3
Pacing time [s]	57 ± 37	54 ± 4	64 ± 10	0.4
Post-procedural complications				
Myocardial infarction	0 (0%)	0 (0%)	0 (0%)	NS
Stroke	1 (1%)	1 (1.2%)	0 (0%)	1.0
Major/life-threatening bleeding	20 (19%)	16 (20%)	4 (17%)	1.0
Major vascular/apical complications	2 (2%)	1 (1.2%)	1 (4.2%)	0.4
New conduction abnormality	4 (3.8%)	2 (2.5%)	2 (8.3%)	0.2
30-days mortality	8 (7.6%)	5 (6.2%)	3 (12.%)	0.4
Post-procedure aortic regurgitation (≥ moderate)	2 (2%)	0 (0%)	2 (8.7%)	< 0.05
Device success	102 (96%)	81 (100%)	21 (87%)	< 0.05

Acute kidney injury occurred more often in TA patients (44%, n = 20, TF: 8%, n = 5; $p < 0.0001$) (Fig. 1A). There was no significant difference in baseline creatinine between the TF and TA groups (99 ± 4 vs. 90 ± 4 umol/L, NS), and there was no difference in baseline estimated glomerular filtration rate (62 ± 2 vs. 59 ± 2 mL/min, NS), hemoglobin (12.4 ± 0.2 vs. 12.2 ± 0.2 g/dL, NS), or volume of contrast used during the procedure (109 ± 9 vs. 126 ± 5 mL, NS, TA vs. TF, respectively). There was a significant difference in total rapid pacing time, with longer rapid pacing in the TA group (TF 44 ± ± 3 vs. TA 75 ± 8 s, $p < 0.0005$).

Procedural characteristics and post-procedural complications are summarized in Table 2.

In multivariate analysis TA TAVI and absence of NAC use pre-procedure were independent predictors of AKI (Table 3).

There was no difference in 30-day mortality between patients with post-procedural AKI and

Table 3. Multivariate logistic regression analysis for predictors of acute kidney injury after transcatheter aortic valve implantation.

Variables	OR	95% CI	P
NGAL	0.99	0.98–1.01	0.24
Creatinine	0.99	0.97–1.01	0.37
Peripheral vascular disease	2.4	0.5–11.9	0.28
TA TAVI	7.0	2.0–29.9	0.002
No NAC pre-procedure	4.7	1.4–18.3	0.01

CI — confidence interval; NAC — N-acetylcysteine; NGAL — neutrophil gelatinase-associated lipocalin; OR — odds ratio; TA TAVI — transapical transcatheter aortic valve implantation

without (12.5% vs. 6.2%, respectively, p = 0.4), but there was a significant difference in overall mortality (Fig. 1B).

Characterization of inflammatory response

Inflammation and oxidative stress. TAVI was associated with a rise in pro-inflammatory cytokines including hsCRP, and TNFα and its receptors (R1 and R2). The magnitude of inflammation was associated with the severity of postprocedural AKI, especially at 44–52 h after the procedure (Fig. 2A, B). The inflammatory response was significantly greater after TA than after TF TAVI (Fig. 3A, D, E, F).

Myeloperoxidase levels rose significantly after TAVI from 540 ng/L at baseline to 992 ng/L at 4–6 h, to 1222 ng/L at 22–26 h, and to 1412 ng/L at 44–52 h (MANOVA, p < 0.0001), suggesting an increase in oxidative stress. Again, these changes were more significant in stages II/III of AKI (Fig. 2B) and after TA TAVI (Fig. 3B).

Interleukin 6 increased significantly after TAVI but to a greater extent in the AKI group (Fig. 4B).

Systemic inflammatory response syndrome was observed in 8 (8%) patients in the TA group (TA 8% vs. TF 0%, p < 0.0005), and of these, 50% had AKI (NS).

Markers of renal injury. Baseline NGAL was significantly higher in the AKI group (Table 1). NGAL levels increased post-procedure in all patients (baseline 115 ± 7 pg/mL vs. 24 h 194 ± ± 11 pg/mL, p < 0.0001), with a greater increase in patients who developed AKI (mean difference, respectively: 67 vs. 11,711 pg/mL, p < 0.005, Fig. 4A).

Cystatin C levels rose significantly and were significantly higher at 44–52 h after TAVI in the group developing AKI (1.18 ± 0.5 vs. 1.71 ± 0.15, p < 0.005).

Markers of myocardial injury. There was no significant difference in myocardial injury between patients with and without AKI (CK-MB: 20 ± 1.7 vs. 23 ± 14, respectively, NS).

Markers of heart failure and neurohormonal activation. We observed a significant increase in ST2 and NT-proBNP after TAVI but with greater

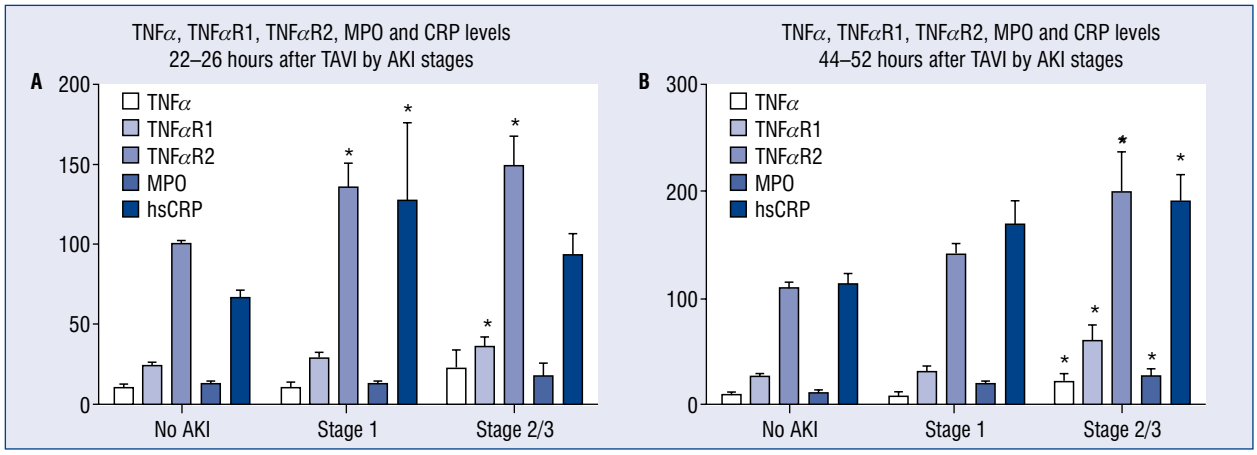

Figure 2. Levels of inflammatory markers and oxidative stress after transcatheter aortic valve implantation (TAVI) by stage of acute kidney injury (AKI); **A.** 22–26 h after TAVI; **B.** 44–52 h after TAVI. One-way ANOVA, followed by Tukey post-hoc test performed if ANOVA was significant, *p < 0.05 from post hoc test significant difference against group with no postprocedural AKI. The magnitude of inflammatory reaction measured by levels of tumor necrosis factor alpha (TNFα) and its receptors, myeloperoxidase (MPO) and C-reactive protein (CRP) 22–26 h after TAVI was higher in all patients who developed AKI regardless of its severity. On the other hand, 44–52 h after TAVI inflammatory markers remained high, but only in patients who developed AKI stage 2/3.

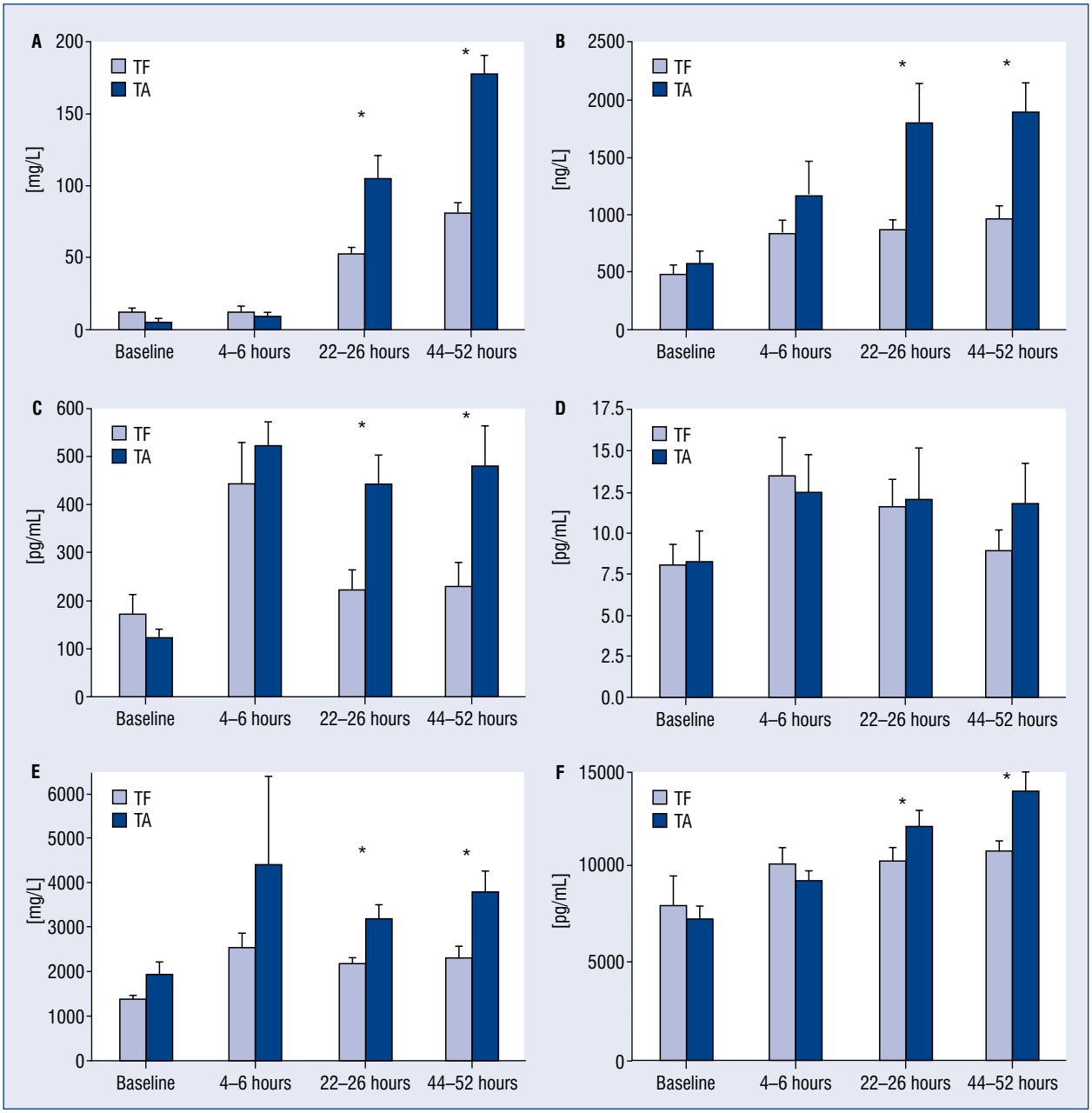

Figure 3. Changes in inflammatory markers and oxidative stress after transfemoral (TF) and transapical (TA) group 4–6 h, 22–26 h, and 44–52 h post-procedure. **A.** High-sensitivity C-reactive protein (hsCRP); **B.** Myeloperoxidase (MPO); **C.** Aldosterone; **D.** Tumor necrosis factor alpha (TNFα); **E.** TNFαR1; **F.** TNFαR2. Two-way ANOVA followed by Bonferroni post hoc test, *$p < 0.05$. Levels of hsCRP, MPO, aldosterone, and TNFαR1 and TNFαR2 were significantly higher after TA transcatheter aortic valve implantation.

changes in the AKI group (Fig. 4C, D). There was no difference in aldosterone levels in the AKI group (not shown), but aldosterone was significantly higher after TA TAVI compared to TF TAVI (Fig. 3C).

Hemodynamic changes. No significant difference was observed in the first 24 h in heart rate, cardiac output, systolic blood pressure, diastolic blood pressure, and mean blood pressure in either group. Systemic vascular resistance was significantly lower at baseline and remained lower in patients who developed AKI (Fig. 5).

Discussion

This is the first study to characterize the inflammatory response associated with TAVI and

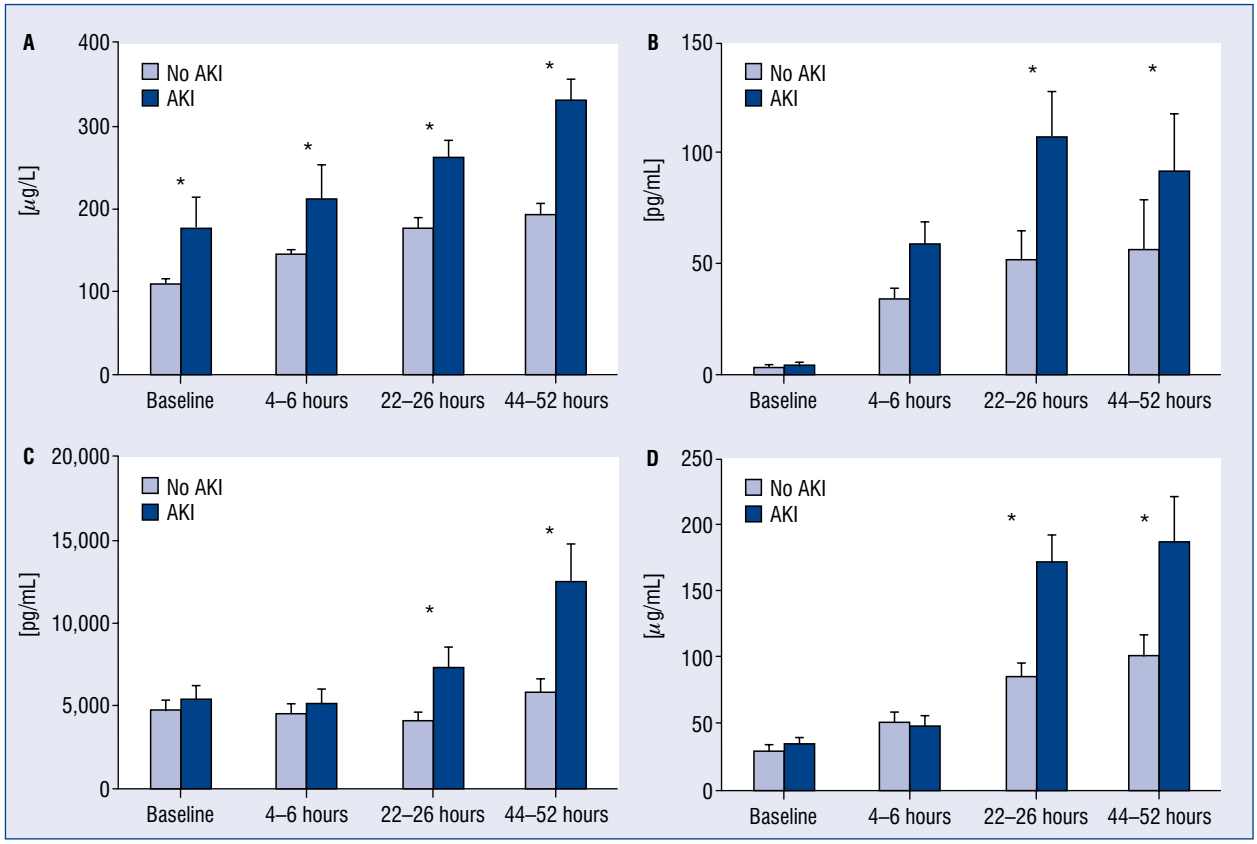

Figure 4. Changes in neurohormonal activation in acute kidney injury (AKI) and no AKI group 4–6 h, 22–26 h, and 44–52 h post-procedure. **A.** Neutrophil gelatinase-associated lipocalin (NGAL); **B.** Interleukin 6; **C.** N-terminal pro-B--type natriuretic peptide (NT-proBNP), **D.** Receptor for interleukin 33 (ST2); Two-way ANOVA followed by Bonferroni post hoc test, *p < 0.05. NGAL levels were higher pre-transcatheter aortic valve implantation (TAVI) and were rising after the procedure significantly more in the AKI group. Interleukin 6 levels increase after TAVI from 4–6 h continuing rise over next hours. The rise in interleukin 6 levels was significantly higher in the AKI group at 22–26 h and 44–52 h. BNP and ST2 levels were rising significantly only in the AKI group at 22–26 h and 44–52 h.

explore its relationship with post-procedural AKI. We have identified pre- and peri-operative risk factors for developing AKI, including peripheral vascular disease, TA approach, and post-TAVI paravalvular aortic regurgitation. Furthermore, there is an association between the risk of AKI and the magnitude of the inflammatory response.

On multivariate analysis, pre-TAVI renal impairment was not associated with post-procedural AKI. Although not powered to show this definitively, our results are in concordance with previously published data [14] from a cohort of 642 patients, divided according to pre-procedural renal function, in which, similarly, pre-procedural renal function was not a predictor of post-procedural AKI. This suggests that factors other than pre-existing renal function contribute to the development of AKI [15].

The association between inflammatory response and AKI after TAVI has been reported in another small study [16], with suggestion of less inflammation with the TF compared with the TA approach [17]. We too observed a greater increase in inflammatory markers and oxidative stress after TA compared with TF TAVI, and that TA TAVI was associated with a significantly greater rate of AKI. Consistent with this, we report a significant increase in pro-inflammatory cytokines (including IL-6 and TNFα receptors), which are involved in the acute phase of the inflammatory response. These pro-inflammatory cytokines activate hepatic synthesis of acute-phase proteins including CRP, which were also significantly increased in our study. This inflammatory reaction has been noted to correlate with AKI and multi-organ failure in other medical settings [8]. Furthermore, the inflammatory response provokes an increase in oxidative stress, which is a known cause of AKI.

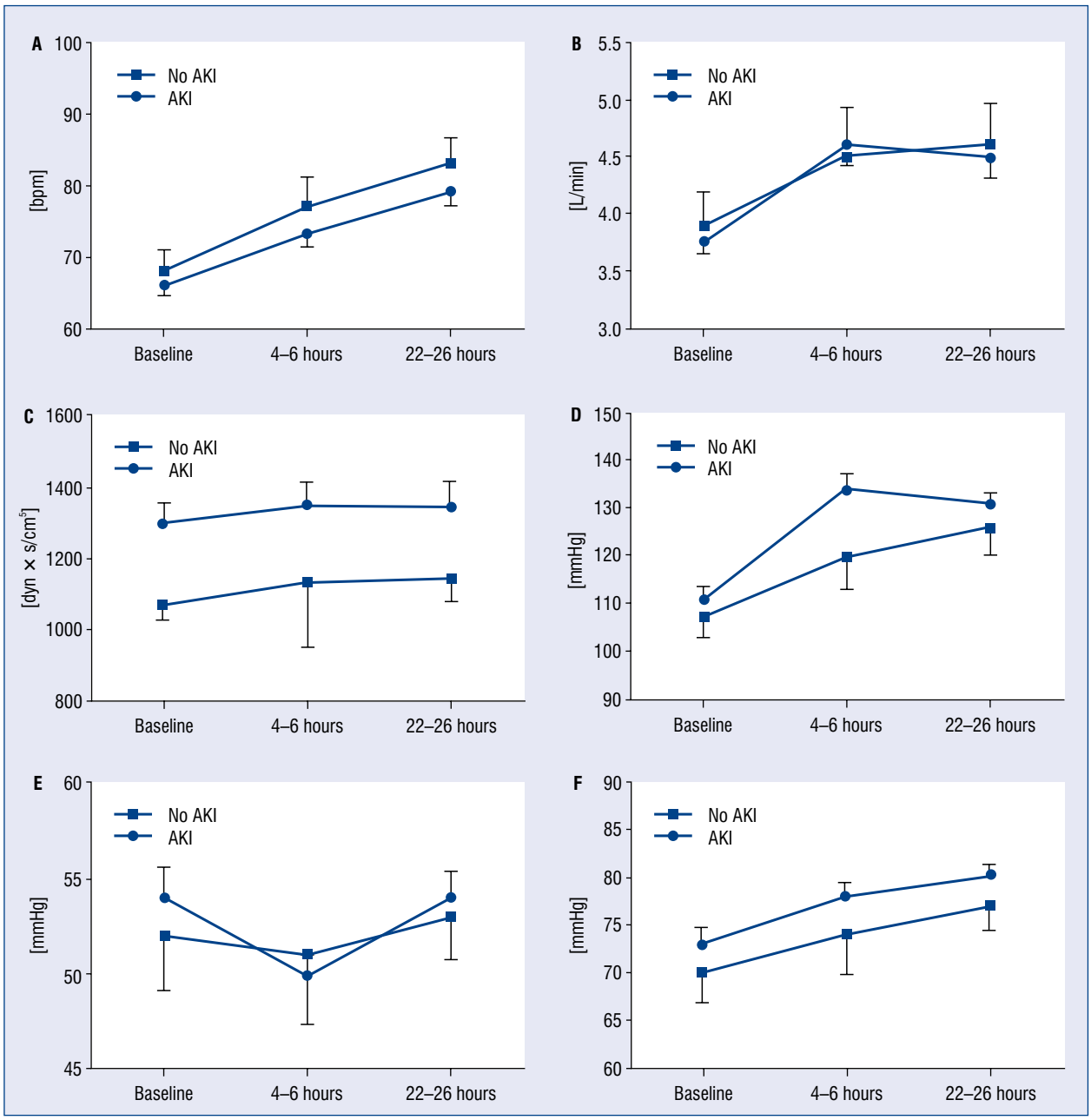

Figure 5. Changes in basic hemodynamics in acute kidney injury (AKI) and no AKI group 4–6 h and 22–26 h post-procedure; **A.** Heart rate (HR); **B.** Cardiac output (CO); **C.** Systemic vascular resistance (SVR); **D.** Systolic blood pressure (SBP); **E.** Diastolic blood pressure (DBP); **F.** Mean blood pressure (MBP). No significant difference was observed in the first 24 h in HR, CO, SBP, DBP, and MBP in either group. The SVR was significantly lower at baseline and remained lower in patients who developed AKI.

Sinning et al. [13] demonstrated that 46% of patients with SIRS develop AKI after TF TAVI, and we similarly found that 50% of patients with SIRS developed AKI. However, SIRS accounted only for 17% of all patients who developed AKI, confirming that lesser inflammatory responses and other factors are clearly important.

Neutrophil gelatinase-associated lipocalin, often labelled a "renal troponin", is a powerful predictor of AKI after onset of cell stressors such as ischemia-reperfusion or inflammation [18]. In the Translational Research Investigating Biomarker Endpoints in AKI study (TRIBE-AKI) elevated NGAL plasma levels predicted AKI and improved

risk stratification [1]. In our cohort, NGAL levels were significantly increased after TAVI, and levels were greater in the TA group. This suggests that significant renal ischemia-reperfusion injury is probably implicated in the development of AKI. We were not able to predict AKI based on measurements of NGAL levels 4–6 h post-TAVI. Interestingly, levels of NGAL were higher at baseline in patients who went on to develop AKI, suggesting a possible predictive value in this setting.

Hemodynamic disturbance may also play a part in renal injury during TAVI. Procedural characteristics such as temporary hypotension during rapid pacing or balloon predilatation, or rhythm disturbances due to aberrant conduction or inotropic support, may be relevant. We, however, found no significant differences in major hemodynamic parameters between the group that developed AKI and those who did not, with no difference in duration of pacing nor size of valve prosthesis. Frequency of rapid pacing, type of prosthesis, and number of attempts to deploy a prosthesis were not examined but may be of interest. We have previously shown that left ventricular (LV) systolic function is transiently impaired post-TAVI, and this phenomenon may well be greater after a TA procedure [12]. Certainly, a longer rapid pacing time in the TA group (utilized by our surgeons for apical closure) can lead to myocardial stunning and transient depression of LV function [12]. More prolonged peri-procedural hypotension with subsequent myocardial damage in addition to myocardial injury related to direct apical access may both serve to activate the inflammatory response, which may explain excess AKI in the TA group.

Using CK-MB, we found no significant difference in myocardial injury between patients with and without AKI. The findings may have been different using troponin, a more specific biomarker for myocardial damage. Koskinas et al. [19] demonstrated the impact of post-procedural cardiac troponin elevation on both 30-day and 2-year prognosis. Mechanisms of troponin release during TAVI are, however, multifactorial, and as well as myocardial injury, they may reflect the complexity of underlying coronary artery disease, concentric LV hypertrophy, peri-procedural particle embolization into the coronary circulation, and pre-existing renal dysfunction. Peripheral vascular disease was more common in the AKI group. A useful extension to the current study would be to include measurements of embolization such as carotid flow and transcranial Doppler to determine the contribution of peripheral embolization in the development of AKI.

B-type natriuretic peptide (BNP) has been shown to be a good predictor of AKI after other forms of cardiac surgery [20] and a general predictor of outcome in patients with AKI [21]. Consistent with previously published data [22] we noticed a significant increase in BNP after TAVI with a greater BNP rise in patients developing AKI. Elevations of BNP may primarily reflect AKI instead of LV dysfunction in this setting. Increased intravascular volume stimulating cardiac secretion and reduced renal clearance of peptides serving as key mechanisms [23–25]. ST2, a member of the interleukin-1 receptor superfamily, was identified as a potential novel biomarker in patients with acute heart failure [26]. ST2 is up-regulated in isolated cardiomyocytes exposed to mechanical strain, and its levels correlate well with acute LV dysfunction independently of BNP [27, 28]. We have previously shown that there is a significant increase in ST2 levels after successful TAVI, perhaps in response to peri-procedural myocardial dysfunction [12]. In the current study we observed a significant increase in ST2 levels in the AKI group, and after TA TAVI more than after TF TAVI. Like BNP, ST2 (by blocking the effects of interleukin-33) has been linked with AKI in other settings [29].

Another important contributor to post-procedural renal ischemia is moderate-severe post-TAVI paravalvular aortic regurgitation, which has previously been linked with AKI and severity associated with higher levels of BNP and troponin [6]. It is now widely accepted that para-prosthetic aortic regurgitation is associated with increased in-hospital and mid-term mortality following TAVI [30–32].

It has been suggested that post-procedural AKI is related to the amount of radio-opaque contrast used during the procedure [4, 14]. This hypothesis was not supported by Kong et al. [16], nor by our data. We did not see any link between volume of contrast used during TAVI and AKI, although all contrast volumes used were low. The volume of contrast was slightly higher in the TF TAVI group, which had a lower risk of AKI.

Tepel et al. [33] reported that NAC may prevent acute renal dysfunction by antioxidant action. NAC acts indirectly by boosting endogenous levels of the major cellular antioxidant, glutathione [34, 35]. Despite proven efficacy in experimental models [36], the use of NAC in preventing AKI after cardiac surgery and coronary angiography in clinical practice remains controversial [37]. There are no data about the effects of NAC on AKI after TAVI. We incidentally observed that patients not given NAC pre TAVI had a higher incidence of

post-procedural AKI, independent of access site and volume of contrast used. This may be influenced by unmeasured confounding factors including the appropriate clinical use in patients perceived to be at higher risk of AKI.

Collectively, these data suggest that the mechanism of AKI is multifactorial and interdependent and seems to involve factors beyond hemodynamic disturbances including the systemic inflammatory response, free radical-induced damage, and ischemia-reperfusion injury.

Limitations of the study

Our study contains only a relatively small number of patients; therefore, certain associations may have been missed, and although the outcome of AKI was examined, the study was not powered to examine differences in temporal trend in development of AKI. Though inflammatory marker elevation parallels AKI development, etiological considerations are made with caution, and further studies are required to delineate underlying mechanisms. The association between AKI and NAC use is incidental and was not a randomized intervention in the study, so again it must be interpreted with caution.

Conclusions

Acute kidney injury after TAVI is predicted by the TA approach and absence of NAC therapy pre-procedure. TAVI generates a significant inflammatory response, with an associated increase in oxidative stress. There is also significant renal ischemia/reperfusion injury.

The changes in these processes are significantly higher after TA TAVI, which may in part explain the higher incidence of AKI in this patient cohort.

Our results inform case selection in this high-risk patient group and emphasize the importance of minimizing tissue damage and hemodynamic instability during the TAVI procedure, thus supporting the technological drive towards a minimally invasive, fully percutaneous procedure. The use of NAC to protect the kidneys merits further study.

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Conflict of interest: None declared

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The Klotho protein supports redox balance and metabolic functions of cardiomyocytes during ischemia/reperfusion injury

Agnieszka Olejnik, Marta Banaszkiewicz, Anna Krzywonos-Zawadzka, Iwona Bil-Lula

Division of Clinical Chemistry and Laboratory Haematology, Department of Medical Laboratory Diagnostics, Faculty of Pharmacy, Wroclaw Medical University, Wroclaw, Poland

Abstract

Background: *Acute heart ischemia followed by reperfusion leads to overproduction of reactive oxygen/nitrogen species (ROS/RNS), disrupted expression of nitric oxide synthase (NOS) and unbalanced glucose metabolism. Klotho is a membrane-bound or soluble protein that exerts protective activity in many organs. While Klotho is produced mainly in the kidneys and brain, it has been recently proven that Klotho is expressed in the cardiomyocytes as well. This study aimed to show the influence of the Klotho protein on oxidative/nitrosative stress and metabolic function of the cardiomyocytes subjected to ischemia/reperfusion (I/R) injury.*

Methods: *Human cardiac myocytes underwent in vitro chemical I/R (with sodium cyanide and 2-deoxy-glucose), in the presence or absence of the recombinant human Klotho protein. The present study included an investigation of cell injury markers, level of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), level of oxidative/nitrosative stress and metabolic processes of the cardiomyocytes.*

Results: *Administration of Klotho protein resulted in mitigation of injury, decreased level of NOX2 and NOX4, reduced generation of ROS/RNS and hydrogen peroxide (H_2O_2), decreased expression of inducible NOS and limited production of nitrates/nitrites in cells under I/R. Glucose uptake and lactate production in the cardiomyocytes subjected to I/R were normalized after Klotho supplementation.*

Conclusions: *The Klotho protein participates in the regulation of redox balance and supports metabolic homeostasis of the cardiomyocytes and hence, contributes to protection against I/R injury.* (Cardiol J 2022; 29, 5: 836–849)

Key words: Klotho protein, cardioprotection, heart, ischemia/reperfusion injury, oxidative stress, nitrosative stress

Introduction

Acute heart ischemia followed by reperfusion (I/R) leads to the interruption of coronary blood flow followed by subsequent restoration of perfusion, resulting in cardiac damage [1]. Heart I/R injury causes an excessive formation of reactive oxygen species (ROS) [2], reactive nitrogen species (RNS), degradation of cardiac contractile proteins by proteolytic enzymes and necrotic cell death [3, 4].

Klotho is a membrane or soluble protein and its protective action is important for the functioning of many organs [5, 6]. Klotho is produced mainly in the kidneys and brain [5, 6]. It was previously shown that a protective, compensatory produc-

Address for correspondence: PhD, DSc, Associate Professor Iwona Bil-Lula, Division of Clinical Chemistry and Laboratory Haematology, Department of Medical Laboratory Diagnostics, Wroclaw Medical University, ul. Borowska 211A, 50–556 Wrocław, Poland, tel: +48 784-06-21, fax: +48 784-00-54, e-mail: iwona.bil-lula@umw.edu.pl

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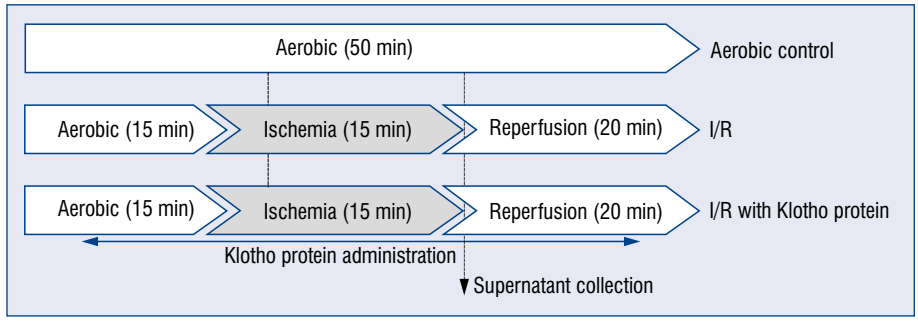

Figure 1. Experimental protocol for in vitro chemical ischaemia/reperfusion (I/R) injury of cardiomyocytes with and without Klotho administration.

tion of Klotho takes place in the cardiomyocytes during I/R. Thus, Klotho was proposed as a biomarker of heart damage [7]. In the current study, it is hypothesised that Klotho could protect the cardiomyocytes from I/R injury and participates in the reduction of formation and activity of such molecules as ROS and RNS. Since lactate is considered an important regulatory molecule of intermediate metabolism involved in I/R, and glucose metabolism is a key process in ischemic heart disease [8, 9]. It is also proposed herein, that Klotho supports the metabolic functions of injured cells.

This study aimed to examine the influence of the Klotho protein on oxidative/nitrosative stress and metabolic functions of the cardiomyocytes subjected to I/R injury.

Methods

Cell culture

The primary human cardiac myocytes (HCM) were purchased from ScienCell Research Laboratories (Carlsbad, CA, USA) and cultured under standard conditions [10] (37°C, water-saturated, 5% CO_2 atmosphere), according to the manufacturer's instructions. Cells were passaged at 90% confluence using 0.25% trypsin-EDTA (Sigma-Aldrich, St. Louis, MO, USA).

The protocol of in vitro chemical I/R injury of cardiomyocytes

Cardiac myocytes in culture underwent in vitro chemical I/R per the guidelines for experimental models of myocardial ischemia and infarction [11]. Figure 1 shows the experimental protocol scheme. Briefly, HCM in the I/R groups underwent 15 min of aerobic stabilization, 15 min of in vitro chemical ischemia and 20 min of reperfusion [3, 7] in the absence or presence of 1 μg/mL [7, 12] of the Recombinant Human Klotho Protein (R&D Systems, 5334-KL-025). The aerobic stabilization and reperfusion were performed in 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) buffer (5.5 mmol/L HEPES, 63.7 mmol/L $CaCl_2$, 5 mmol/L KCl, 2.1 mmol/L $MgCl_2$, 5.5 mmol/L glucose, 10 mmol/L taurine) containing additional 55 μmol/L $CaCl_2$ and 0.75 mg/mL BSA. During in vitro chemical ischemia, cells were incubated in HEPES buffer containing 4.4 mmol/L 2-deoxyglucose (to inhibit glycolysis) and 4.0 mmol/L sodium cyanide (cellular respiration inhibitor) [3]. The optimal ischemia duration (15 min) was previously established experimentally by measuring the activity of lactate dehydrogenase (LDH) released from cells as a marker of cell injury (data not shown). In the Klotho experimental group (I/R+Klotho), cells underwent I/R procedure in the presence of Klotho protein in the buffers (1 μg/mL final concentration) during the entire protocol. Cells from the aerobic control group were incubated aerobically for 50 min in HEPES buffer at real time (RT). Then, cells from all groups were homogenized mechanically with a hand-held homogeniser in the homogenization buffer.

Klotho mRNA expression

The total RNA from HCM was isolated with TRIZOL reagent (Thermo Fisher Scientific, Waltham, MA, USA) according to the manufacturer's instructions. A microvolume ultraviolet spectrophotometer (NanoDrop Lite, Thermo Scientific) was used to evaluate the concentration and purity of RNA. To prepare cDNA, reverse transcription of pure RNA samples (100 ng) was conducted using the iScript cDNA Synthesis Kit (BioRad, Hercules, CA, USA), according to the instructions provided. The reverse transcription was carried out at 42°C for 30 min and inactivated at 85°C for 5 min. Real-time quantitative polymerase chain reaction (RT-qPCR) and CFX96 Real-Time System

(BioRad) were used for the analysis of the Klotho gene expression. The expression level of glucose--6-phosphate dehydrogenase (G6PD) gene was used as an internal reference. The final volume of the reaction mix was 30 μL and included iTag Universal Sybr Green Supermix with ROX (BioRad), forward and reverse primers (250 nmol/L final conc.), water and cDNA (100 ng). The primers were designed by us and synthesized by TIB Molbiol (TIB Molbiol, Berlin, Germany). The amount of Klotho mRNA relative to G6PD was calculated as $2^{-\Delta Ct}$.

Klotho protein production

The concentration of Klotho protein in cell homogenates was measured using Sandwich Human Klotho ELISA Kit from Biorbyt (orb397071, Biorbyt Ltd., UK), according to the manufacturer's instructions. The color strength in each well was proportional to the quantity of Klotho protein and was normalized to total protein concentration.

LDH activity measurement

A Lactate Dehydrogenase Activity Assay Kit (Sigma-Aldrich, St. Louis, MO, USA) was used to determine the activity of LDH in cells, according to the manufacturer's instructions. LDH is a stable cytosolic enzyme that is released upon membrane damage/permeability or cell lysis and serves as a marker of cell damage. LDH activity was assessed in cell supernatants and normalized to total protein concentration.

The level of NOX2 and NOX4

To assay nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2 (NOX2) and NADPH oxidase 4 (NOX4) expression in the cardiomyocytes, Human NADPH Oxidase 2 (NOX2) ELISA Kit and Human NADPH Oxidase 4 (NOX4) ELISA Kit (all from SunLong Biotech Co., Zhejiang, China) in accordance to the manufacturer's instructions were used. These ELISA kits use Sandwich-ELISA as the method. The optical density was measured spectrophotometrically at a wavelength of 450 nm. The optical density values were proportional to the concentration of NOX2 and NOX4, respectively. NOX2 and NOX4 levels were assessed in cell supernatants and normalized to total protein concentration in each sample.

Assessment of oxidative and nitrosative stress

An OxiSelect™ In Vitro ROS/RNS Assay Kit (Cell Biolabs, San Diego, USA) was used to assess the influence of Klotho on the levels of total ROS/RNS and hydrogen peroxide (H_2O_2) in the cardiomyocytes. The assay measures total ROS/RNS or H_2O_2 using a proprietary fluorogenic probe — dichlorodihydrofluorescein (DCFH) DiOxyQ. In the presence of ROS and RNS, the DCFH is rapidly oxidised to the highly fluorescent 2',7'-dichlorodihydrofluorescein. The DCFH-DiOxyQ probe can react with H_2O_2, peroxyl radical ($ROO\cdot$), nitric oxide (NO), and peroxynitrite anion ($ONOO^-$). These free radical molecules are representative of both ROS and RNS, thus allowing for the measurement of the total free radical population within a sample. Using the H_2O_2 standards and standard curve, the level of H_2O_2 was also assessed. Fluorescence intensity was proportional to the total ROS/RNS or H_2O_2 levels within the sample. Total ROS/RNS and H_2O_2 levels were assessed in cell supernatants and normalized to total protein concentration. However, there are some limitations in the use of DCFH, for example, DCFH does not directly react with H_2O_2 to form the fluorescent product [13]. Therefore, DCFH results were interpreted as an indirect measure of H_2O_2.

Measurement of TAC of cardiomyocytes

An OxiSelect™ Total Antioxidant Capacity Assay Kit (Cell Biolabs, San Diego, USA) was used to assess the influence of Klotho on the oxidative stress inhibition during I/R. Measurement of the total non-enzymatic antioxidant capacity is indicative of the cells' ability to counteract induced oxidative stress. Total antioxidant capacity (TAC) assay is based on the reduction of copper (II) to copper (I) by the antioxidants present in the sample. The TAC level was measured in cell homogenates, expressed as μM of Copper Reducing Equivalents (CRE) and normalized to μL of cell homogenates.

Immunofluorescence staining for iNOS

Human cardiac myocytes were cultured in a 96-well plate at a density of 5.5×10^3 cells per well for 24 h, and then subjected to in vitro chemical I/R according to the protocol shown in Figure 1. Then, cells were subjected to fixation at RT for 15 min, with 500 μL/well of 4% paraformaldehyde and were incubated with a blocking buffer for 1 h at RT. Primary antibodies, mouse anti-inducible nitric oxide synthase (iNOS) 1:1000 (ab21775, Abcam, UK), were incubated at 4°C overnight and then washed with phosphate buffered saline (PBS). Then, the secondary antibodies — goat anti-mouse IgG 1:500 (ab96872, Abcam, UK) labelled with DyLight® 550 — were added and incubated at RT for 45 min. Myocytes were stained with DAPI (4',6-diamidino-

2-phenylindole, Sigma-Aldrich) 1:1000 for 15 min in the dark and rinsed with PBS to visualize the cells' nuclei. A Spark Multimode Microplate Reader (Tecan Trading AG, Switzerland) was used to read the signal emitted. To visualize the expression of iNOS (red fluorescence), Thunder Leica Imager (Leica Microsystems) was used. The number of cells was assessed by measuring the fluorescence of the cells' nuclei stained by DAPI (blue fluorescence). The expression of iNOS protein in the aerobic and I/R groups was assessed by measuring red fluorescence intensity expressed in arbitrary units (AU) and normalized to the number of cells (blue fluorescence) in each well.

Nitrates and nitrites ($(NO_x)^-$) level

The amount of total $(NO_x)^-$ (oxidative products of endogenous NO) in cells serves as a measure of NO production [3, 14]. A commercially available Nitric Oxide Assay Kit (Abcam, Cambridge, MA, USA) according to the manufacturer's instructions for measurement of $(NO_x)^-$ level was used. The $(NO_x)^-$ level was assessed in cell homogenates and normalized to total protein concentration.

The measurement of glucose uptake and lactate production in cardiomyocytes

To assess the metabolic status of cells, glucose uptake and lactate production were measured. 2-deoxyglucose (2DG) uptake was studied using a bioluminescent Glucose Uptake-Glo™ Assay (Promega, Madison, WI, USA). Briefly, 2DG is taken up by glucose transporters and metabolized to 2-DG-6-phosphate (2DG6P) in the same manner as glucose. 2DG6P cannot be further metabolized, and thus accumulates within the cells. Accumulated 2DG6P is directly proportional to 2DG (or glucose) uptake by cells and the luminescence is proportional to the concentration of 2DG6P. HCM were cultured in a 96-well plate at a density of 5.5×10^3 cells per well for 24 h and then subjected to in vitro chemical I/R injury according to the protocol shown in Figure 1. The cell confluence in each well was measured. Afterwards, 50 μL of 1 mM 2DG per well for 10 min was added and accumulated 2DG6P was measured using a luminescence assay, according to the manufacturer's guidelines. Data were normalized to the percent of cell confluence and expressed in relative light units (RLU) in the case of each well. Lactate production in the cardiomyocytes was examined using an L-Lactate Assay Kit (ab65331, Abcam, UK) according to the manufacturer's instructions. The lactate concentration was assessed in cell supernatants and normalized to total protein concentration.

Determining the total protein concentration

The Bradford method [15] was used to determine protein concentration in cell homogenates and supernatants. Bio-Rad Protein Assay Dye Reagent (BioRad) and Spark Multimode Microplate Reader (Tecan Trading AG, Switzerland) for measuring total protein concentration were used.

Statistical analysis

GraphPad Prism 6 software (GraphPad Software, San Diego, CA, USA) was used for statistical analysis of the results. To assess the normality of variance changes, either the Shapiro-Wilk normality test or the Kolmogorov-Smirnov test was used. Then, ANOVA or nonparametric test with post hoc tests for comparison of data between measurement groups were used. Correlations were assessed using the Pearson or Spearman test, as appropriate. Results were expressed as mean ± standard error of mean (SEM), with a value of $p < 0.05$ being regarded as statistically significant.

Results

Reduced injury of cardiac cells in the presence of Klotho

The expression of the Klotho gene (Fig. 2A) and the production of the Klotho protein (Fig. 2B) were increased in cells subjected to I/R in comparison to the aerobic control group. LDH activity in supernatants was significantly higher in the I/R group compared to the aerobic (Fig. 2C). The expression of the Klotho gene positively correlated with LDH activity ($p = 0.0001$, $r = 0.63$) (Fig. 2D). The administration of exogenous recombinant human Klotho protein during I/R, regulated the expression of the Klotho gene (Fig. 2A) and protein (Fig. 2B) in the cardiomyocytes, and significantly reduced their damage (Fig. 2C).

The level of NOX2 and NOX4 in cell supernatants

The level of NOX2 was significantly higher in cells injured by I/R (Fig. 3A). NOX2 level (Fig. 3A) and NOX4 level (Fig. 3B) were lower in the I/R+ Klotho group in comparison to I/R. Additionally, the administration of Klotho during I/R resulted in a lower NOX4 level than in cells maintained in aerobic conditions (Fig. 3B). The expression

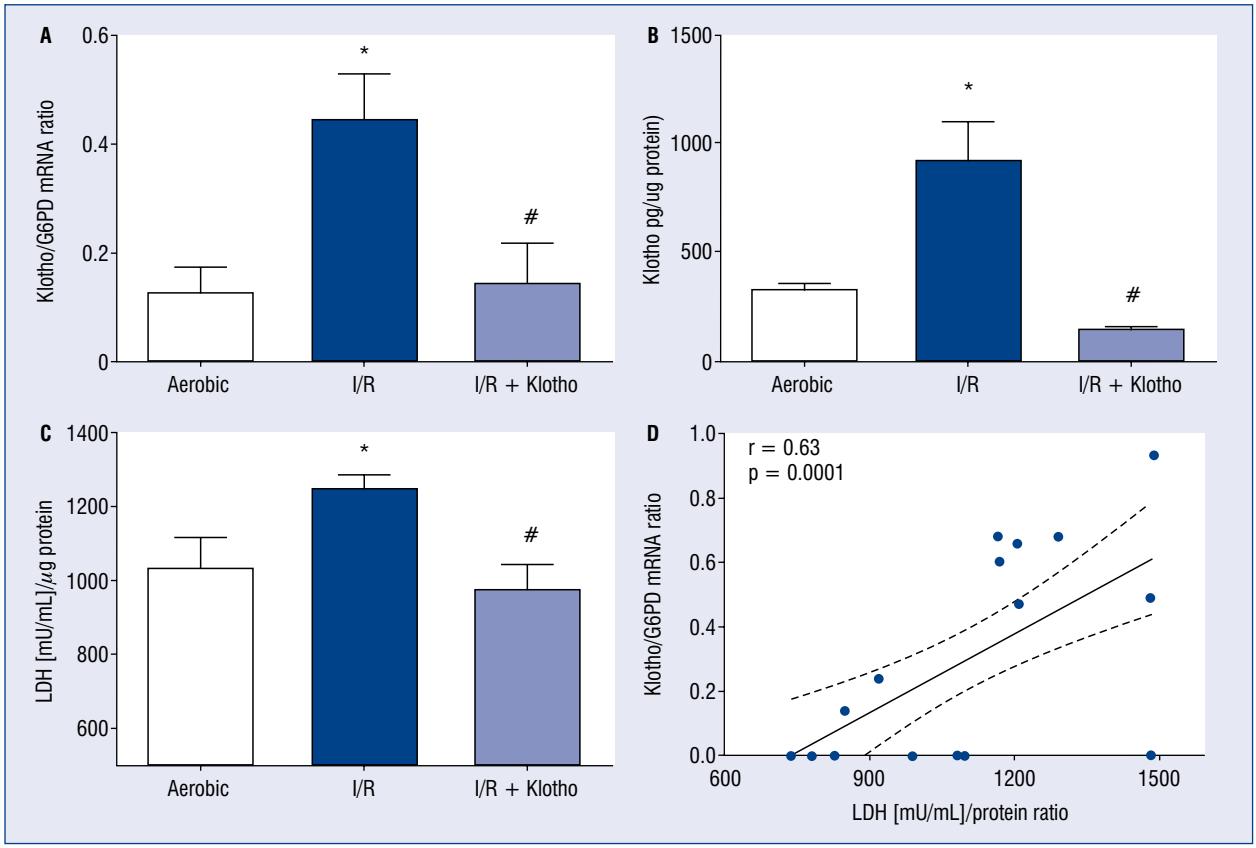

Figure 2. The expression of Klotho gene and protein in the cardiomyocytes during ischemia/reperfusion (I/R) injury. **A.** The expression of the Klotho gene in human cardiomyocytes was examined by real time quantitative polymerase chain reaction (RT-qPCR) and normalized to glucose-6-phosphate dehydrogenase (G6PD); **B.** The production of the Klotho protein in the cardiomyocytes tested by ELISA; **C.** Lactate dehydrogenase (LDH) activity in cell supernatants as a marker of cell death. LDH activity was normalized to the total protein concentration; **D.** Correlation of the Klotho gene expression and LDH activity; mU/mL — milli international enzyme units per milliliter; *p < 0.05 vs. the aerobic control group; #p < 0.05 vs. ischemia/reperfusion; mean ± SEM; n = 8–20.

of NOX2 in the cardiomyocytes was about 9-fold higher than the expression of NOX4.

Reduced oxidative and nitrosative stress in cardiac cells treated with Klotho

The total ROS and RNS level (Fig. 4A) and H_2O_2 level (Fig. 4B) were significantly higher in the I/R group compared to the aerobic control group. There was a positive correlation between total ROS/RNS and H_2O_2 levels ($r = 0.94$, $p < 0.0001$) (Fig. 4C). The administration of Klotho protein effectively reduced the production of ROS/RNS (Fig. 4A) and H_2O_2 (Fig. 4B), and enhanced TAC (Fig. 5A) of cells subjected to I/R. TAC of the cardiomyocytes negatively correlated with LDH activity ($r = –0.46$, $p = 0.0106$; Fig. 5B), ROS/RNS level ($r = –0.49$, $p = 0.0278$; Fig. 5C), H_2O_2 level ($r = –0.73$, $p < 0.0001$; Fig. 5D), and with NOX2 ($r = –0.49$, $p = 0.0409$) and NOX4 ($r = –0.65$, $p = 0.0037$) levels (Fig. 5E).

The expression of iNOS protein in cardiomyocytes

The expression of iNOS protein in the cardiomyocytes tested by immunofluorescence staining was significantly enhanced in the I/R group compared to the aerobic control group (Fig. 6A, 6D). There was a positive correlation between the iNOS expression and the ROS/RNS level ($r = 0.59$, $p = 0.0075$; Fig. 6B) and H_2O_2 level ($r = 0.59$, $p = 0.0018$; Fig. 6C). Klotho supplementation during I/R reduced the expression of iNOS in the cardiomyocytes (Fig. 6A, 6D).

The production of NO in cardiac cells

The amount of total $(NO_x)^-$ served as the measure of NO production. The level of $(NO_x)^-$ was significantly higher in cells subjected to I/R compared to the aerobic group (Fig. 7A). The level of $(NO_x)^-$ positively correlated with LDH activity

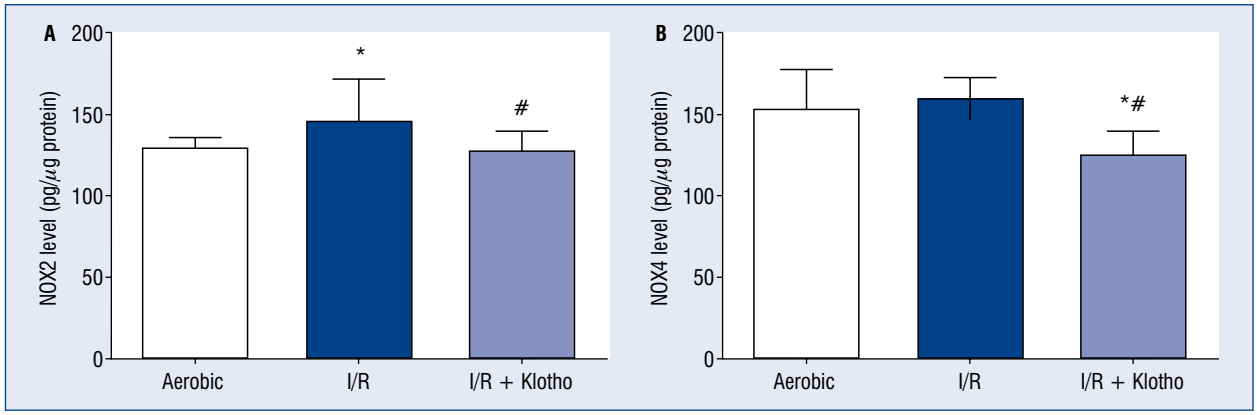

Figure 3. The level of NADPH oxidase 2 (NOX2) and NADPH oxidase 4 (NOX4) in cell supernatants. **A.** The level of NOX2 in cell supernatants normalized to total protein concentration; **B.** The level of NOX4 in cell supernatants normalized to total protein concentration; NADPH — nicotinamide adenine dinucleotide phosphate; *p < 0.05 vs. aerobic control; #p < 0.05 vs. ischemia/reperfusion (I/R); mean ± SEM; n = 7–16.

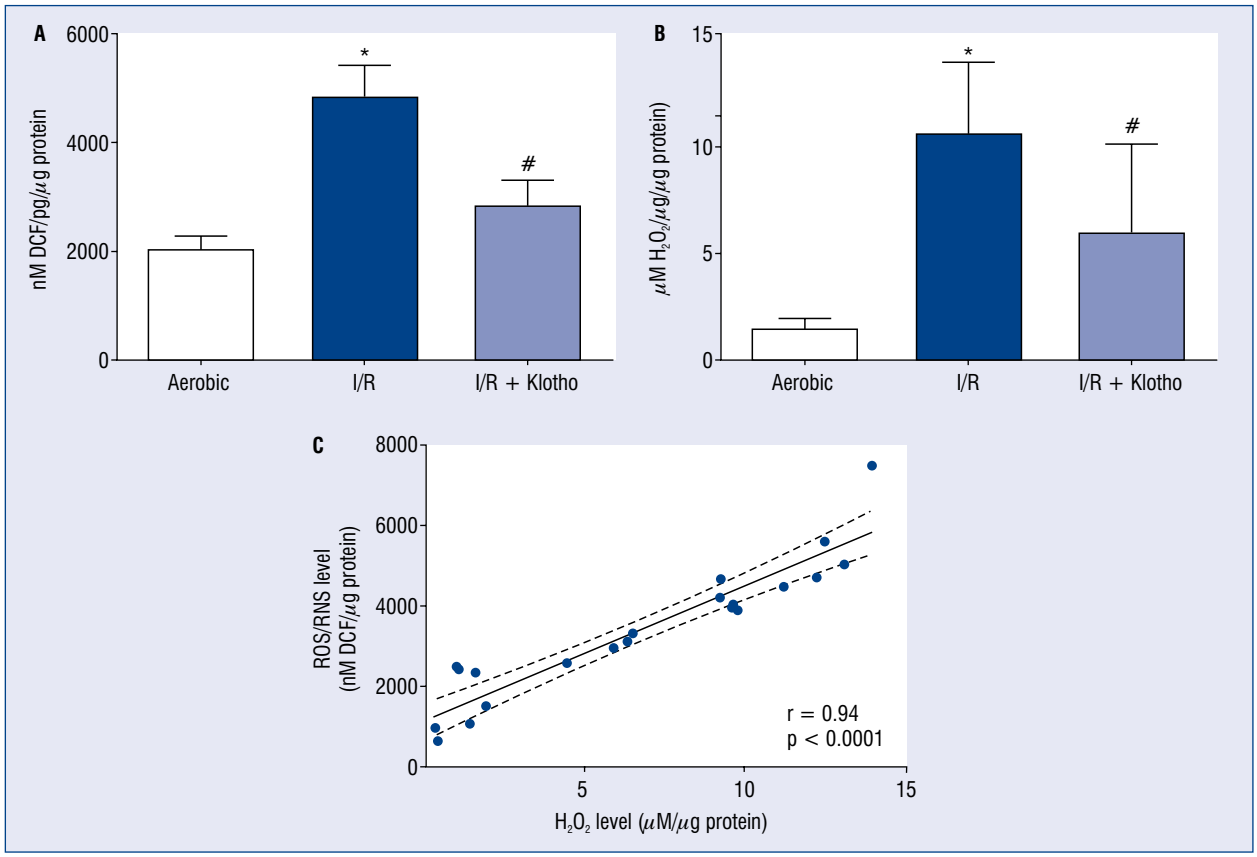

Figure 4. Oxidative and nitrosative stress in cardiac cells. **A.** The total reactive oxygen species (ROS) and reactive nitrogen species (RNS) level in cell supernatants expressed as nM of 2′, 7′-dichlorodihydrofluorescein (DCF) and normalized to total protein concentration; **B.** The level of hydrogen peroxide (H_2O_2) in cell supernatants normalized to total protein concentration; **C.** Correlation of ROS/RNS and H_2O_2 level; *p < 0.05 vs. aerobic control; #p < 0.05 vs. ischemia/reperfusion; mean ± SEM; n = 5–10.

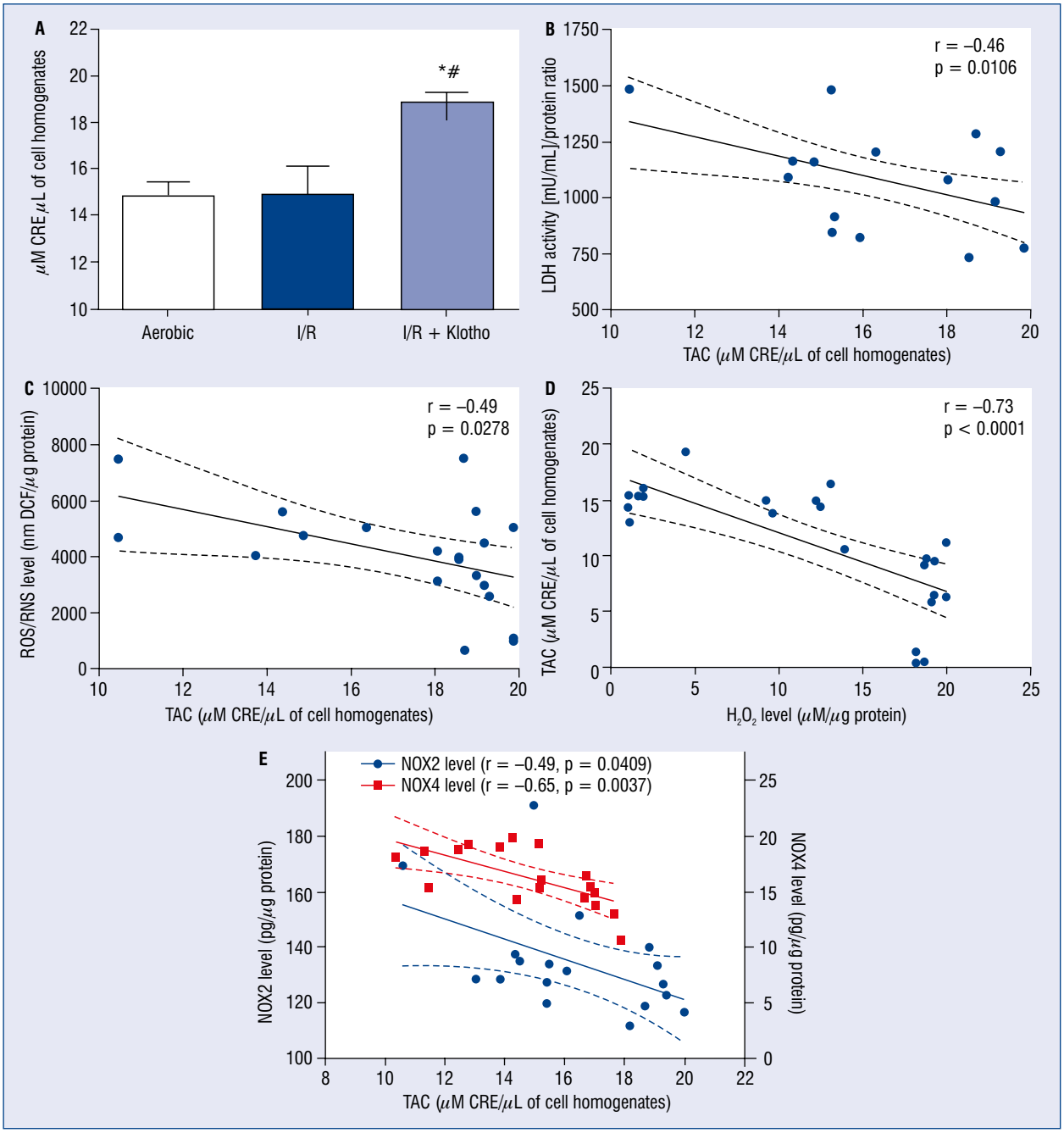

Figure 5. Antioxidant defence in cardiac cells; **A.** Total antioxidant capacity (TAC) of the cardiomyocytes. TAC was expressed as μM of Copper Reducing Equivalents (CRE) and normalized to μL of cell homogenates; **B.** Correlation between TAC and lactate dehydrogenase (LDH) activity in the aerobic, ischemia/reperfusion (I/R) and I/R + Klotho groups; **C.** Correlation between TAC and reactive oxygen species/reactive nitrogen species (ROS/RNS) level in the I/R and I/R + Klotho groups; **D.** Correlation between TAC and hydrogen peroxide (H_2O_2) level; **E.** Correlation between TAC, NOX2 and NOX4 levels; DCF — 2′, 7′-dichlorodihydrofluorescein; mU/mL — milli international enzyme units per milliliter; NADPH — nicotinamide adenine dinucleotide phosphate; NOX2 — NADPH oxidase 2; NOX4 — NADPH oxidase 4; *p < 0.05 vs aerobic control; #p < 0.05 vs. I/R; mean ± SEM; n = 6.

(r = 0.39, p = 0.0318) and ROS/RNS level (r = 0.42, p = 0.0130; Fig. 7B), and with NOX2 (r = 0.47, p = 0.0050) and NOX 4 (r = 0.50, p = 0.0026) levels (Fig. 7C). The administration of Klotho protein during I/R reduced the production of $(NO_x)^-$ (Fig. 7A).

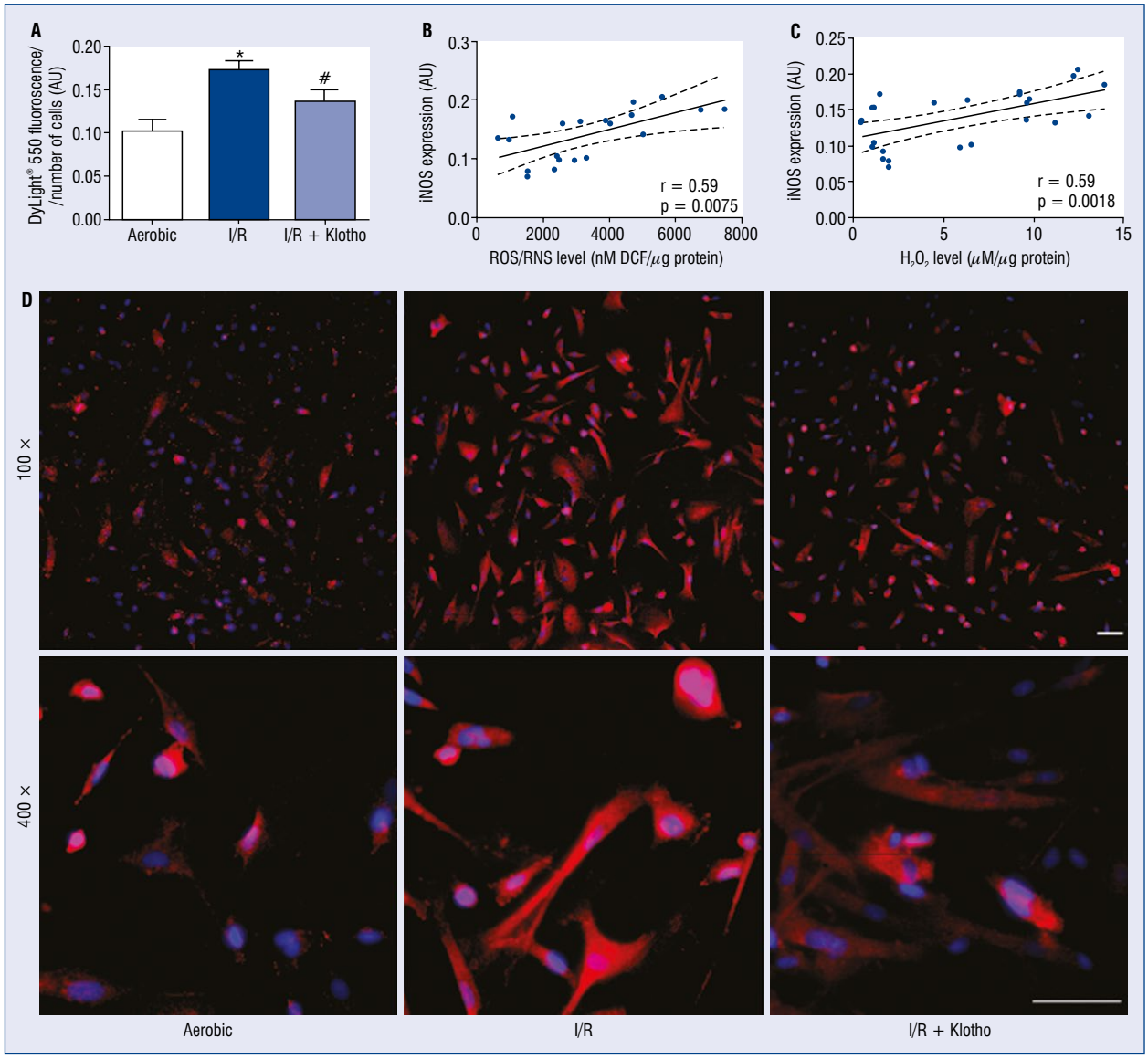

Figure 6. The expression of inducible nitric oxide synthase (iNOS) protein in cardiomyocytes; **A.** The expression of iNOS protein in the cardiomyocytes; **B.** Correlation between the iNOS expression and the reactive oxygen species/reactive nitrogen species (ROS/RNS) level; **C.** Correlation between iNOS expression and hydrogen peroxide (H_2O_2) level; **D.** Immunofluorescence staining of cardiomyocytes for iNOS (red fluorescence) and 4′,6-diamidino-2-phenylindole (DAPI) for nuclei (blue fluorescence). The expression of iNOS was expressed as arbitrary units (AU) and normalized to total number of cells (blue fluorescence). Graph bars show the average of total cell fluorescence in each experiment; magnification 100× and 400×; scale bar 100 μm; DCF — 2′, 7′-dichlorodihydrofluorescein; AU — arbitrary units; *$p < 0.05$ vs. aerobic control; #$p < 0.05$ vs. ischemia/reperfusion (I/R); mean ± SEM; n = 7–8.

Metabolic status of cardiomyocytes subjected to I/R injury

The glucose uptake was reduced in cells from the I/R group in comparison to the aerobic control group (Fig. 8A) and negatively correlated with LDH activity ($p = 0.0002$, $r = –0.65$) (Fig. 8B). The production of lactate was also increased in the cardiomyocytes subjected to I/R compared to the aerobically maintained cells (Fig. 8C). Lactate production positively correlated with LDH activity ($p = 0.03$, $r = 0.39$) and ROS/RNS level ($p = 0.0033$, $r = 0.64$) (Fig. 8D). The administration of Klotho protein normalized glucose uptake (Fig. 8A) and lactate production (Fig. 8C) in cells subjected to I/R.

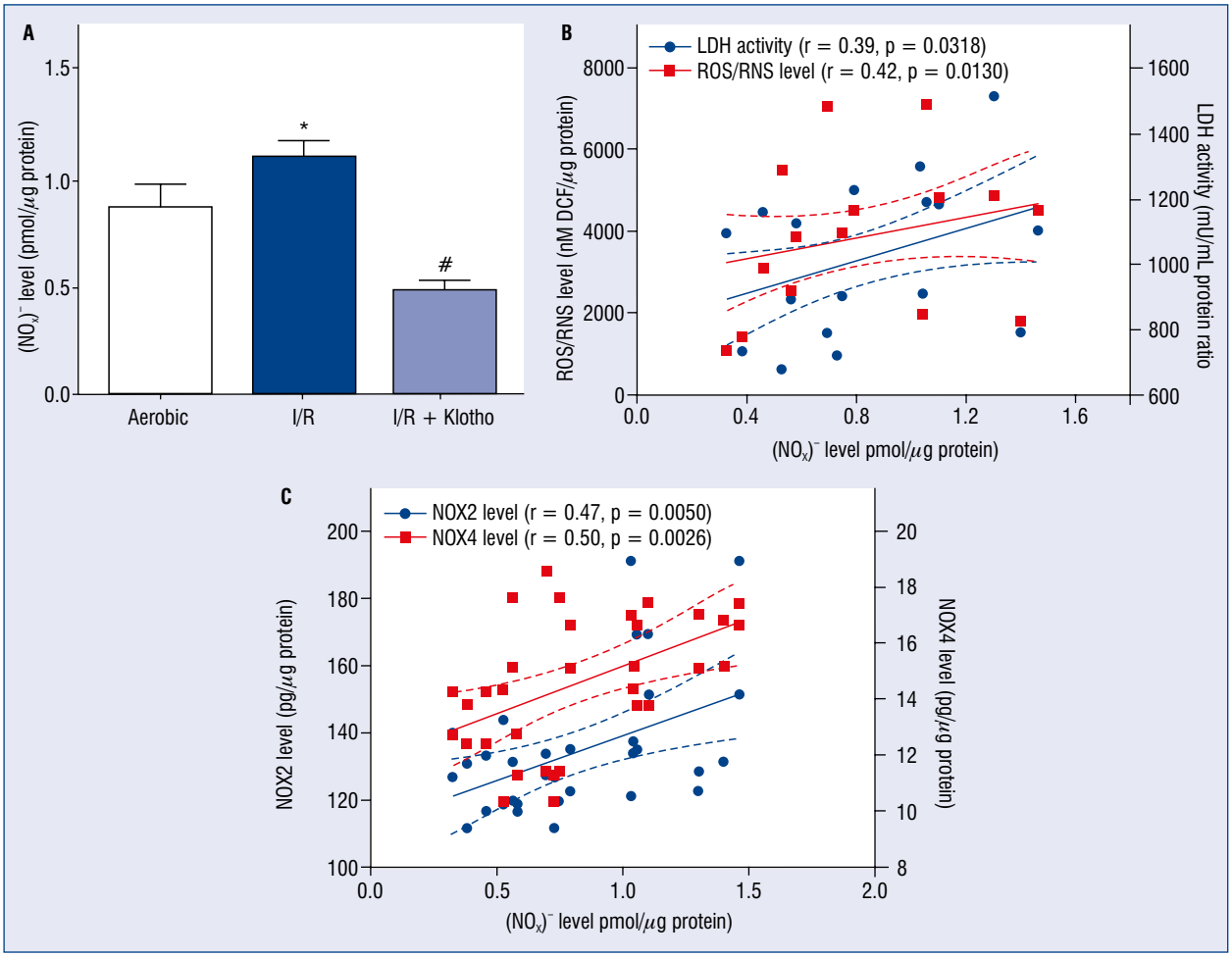

Figure 7. The production of nitric oxide (NO) in cardiomyocytes; **A.** The level of total nitrate/nitrite $(NO_x)^-$ in cardiac cells as an indicator of NO production. The level of $(NO_x)^-$ in cell homogenates was normalized to total protein concentration; **B.** Correlation between $(NO_x)^-$ level, lactate dehydrogenase (LDH) activity and reactive oxygen species/ /reactive nitrogen species (ROS/RNS) level; **C.** Correlation between $(NO_x)^-$, NOX2 and NOX4 levels; DCF — 2′, 7′-dichlorodihydrofluorescein; mU/mL — milli international enzyme units per milliliter; NADPH — nicotinamide adenine dinucleotide phosphate; NOX2 — NADPH oxidase 2; NOX4 — NADPH oxidase 4; $(NO_x)^-$ — nitrates and nitrites; *p < 0.05 vs. aerobic control; #p < 0.05 vs. ischemia/reperfusion (I/R); mean ± SEM; n = 10–12.

Discussion

Recent studies have shown that Klotho acted in a preventive and therapeutic way in acute renal failure, chronic kidney disease, and ischaemic brain injury [15–20]. For this reason, the present study hypothesised that Klotho protein may contribute to the functioning of a compensatory mechanism that mitigates the initial damage in the heart tissue as well. The current research revealed that Klotho protein participates in the reduction of oxidative/ /nitrosative stress and supports metabolic functions in the cardiomyocytes, showing that Klotho contributes to cardioprotection.

It was proven that higher serum Klotho level correlated with reduced occurrence of cardiovascular events and cardiovascular death in humans [21]. An increased level of the serum Klotho in patients who have had myocardial infarction was observed, and as such, the compensatory production of Klotho to prevent the development of subsequent heart lesions was suggested [22]. Importantly, it was previously shown that a compensative production of the Klotho protein takes place in the cardiomyocytes during I/R to protect cells from further injury [7]. In the current study, increased cell injury in the cardiomyocytes subjected to I/R was shown. The expression of the Klotho gene and protein were

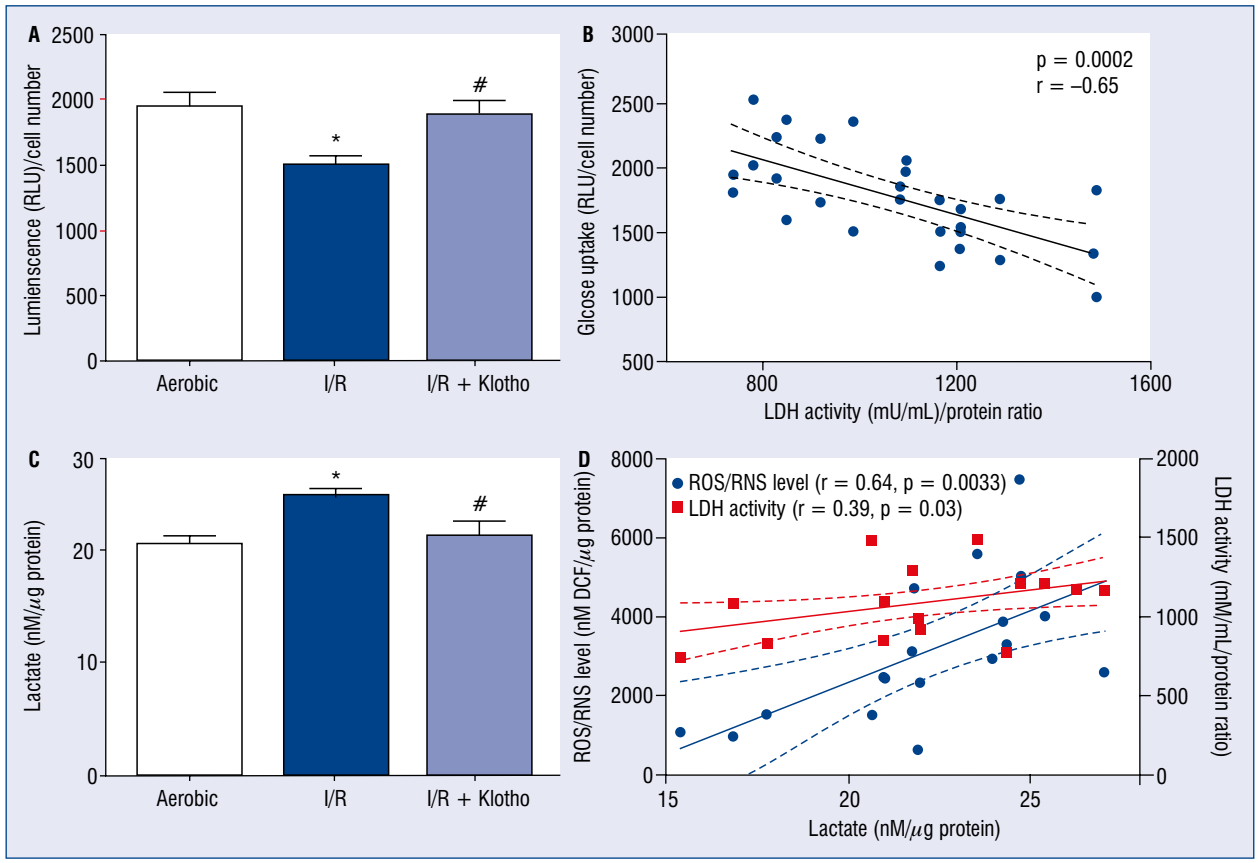

Figure 8. Metabolic status of cardiomyocytes during ischemia/reperfusion (I/R) injury. **A**. The glucose uptake in the cardiomyocytes subjected to I/R with or without Klotho supplementation. The data were expressed in relative lights units (RLU) and normalized to the cell number in each well; **B**. Correlation between glucose uptake and lactate dehydrogenase (LDH) activity; **C**. The influence of I/R injury and Klotho protein on the production of lactate in the cardiomyocytes. The lactate concentration was assessed in cell supernatants and normalized to total protein concentration; **D**. Correlation between lactate level, LDH activity and reactive oxygen species/reactive nitrogen species (ROS/RNS) level; DCF — 2′, 7′-dichlorodihydrofluorescein; mU/mL — milli international enzyme units per milliliter; *p < 0.05 vs. aerobic control; #p < 0.05 vs. I/R; mean ± SEM; n = 5–10.

significantly increased in I/R group and positively correlated with cell damage, suggesting a compensatory expression of Klotho to counteract the injury. Administration of the exogenous recombinant human Klotho protein during I/R regulated the expression of the Klotho gene and production of the Klotho protein in cardiomyocytes to the level observed in aerobic conditions. Herein, it is implied that this change may be due to a negative feedback loop in response to the presence of the exogenous Klotho protein, that requires further investigation. Similarly, Sahu et al. (2018) [23] showed that the expression of the Klotho in the muscles was increased in young mice following an acute cardiotoxin-induced injury. Thus, we suggest that the administration of the Klotho protein may contribute to prevention of damage and reduction of injuries in the cardiomyocytes.

An increasing oxidative stress in the failing heart is mainly caused by inactivation of complex I and the functional uncoupling of the respiratory chain in mitochondria. However, the activity of enzymes like xanthine oxidase, cyclooxygenase, NOS, and NOX is also a source of ROS [24]. NOX is a membrane-bound enzyme complex with activity in the extracellular space. NOX isoforms catalyze production of a superoxide free radical and other ROS, thus representing an important source of ROS [25]. While NOX2 is often referred to as the phagocyte NADPH oxidase, it is also expressed in neurons, cardiomyocytes, skeletal muscle myocytes, hepatocytes, endothelial cells and hematopoietic stem cells, and mainly generate superoxide. NOX4 is highly expressed in the kidney and is responsible for basal H_2O_2 production [25, 26]. It is known that NOX mediates oxidative stress during

heart, kidney, brain, liver, and lung I/R injury [27]. Moreover, it was reported that NOX2 and NOX4 play an important role in myocardial hypertrophy and/or cardiac remodeling [28]. In the present analysis, the level of NOX2 was significantly higher in I/R cells, while Klotho protein contributed to the reduction of NOX2 and NOX4 expression during I/R. Similarly, an increased NOX2 expression in human cardiomyocytes after acute myocardial infarction was shown [29]. The level of NOX2 and NOX4 was upregulated in a guinea pig model of progressive left ventricular hypertrophy or in the failing heart in mice [24, 30]. As reported, Klotho decreased NOX2 protein expression in rat aorta smooth muscle cells by influencing the cAMP/ /protein kinase A pathway [31]. A recent study showed that treatment with Klotho suppressed NOX2 and NOX4 expression and inhibited p38 and extracellular signal-regulated protein kinase 1/2 signalling pathways, thus protecting against indoxyl sulphate-inducted myocardial hypertrophy in mice [28]. In the present study, it was observed that Klotho effectively reduced NOX2 and NOX4 expression in I/R injured cardiomyocytes, suggesting cardioprotection. However, it needs to be emphasized that it was preliminary research on Klotho and NOX, thus further analysis to reveal the potential mechanism is needed.

Research over the last few years has revealed that Klotho limited oxidative stress, inflammation and fibrosis in HeLa, as well as in the aortic or renal murine cells [32, 33]. It was shown that Klotho led to the activation of the forkhead box protein O transcription factors through the inhibition of insulin/insulin growth factor 1/phosphatidylinositol 3-kinase signalling pathway. It resulted in enhanced expression of superoxide neutraliser manganese superoxide dismutase, and consequently, in oxidative stress resistance [32, 33]. Therefore, it was of interest to investigate whether the administration of a recombinant Klotho protein may limit oxidative stress in cardiac cells as well. An increased production of ROS/RNS and H_2O_2 was shown in the cardiomyocytes subjected to I/R. Cardiomyocyte supplementation with exogenous Klotho protein during I/R contributed to the reduction of oxidative stress, suggesting the antioxidative potential of Klotho. It was subsequently observed that the TAC of the cardiomyocytes negatively correlated with LDH activity and with ROS/RNS, H_2O_2, NOX2, and NOX4 levels, confirming that the intensified damage to heart cells during I/R is due to an unbalanced increase in ROS/RNS level, while administration of Klotho significantly enhanced antioxidant activity. This resulted in the reduction in injury and maintenance of cardiomyocyte function. In addition, studies have shown a decrease in ROS formation, reduced oxidative stress and apoptosis after Klotho protein administration or induction of the Klotho gene expression in the kidneys and brain [12, 16, 20, 33, 34]. Proposed herein, that Klotho may also support protection of the cardiomyocytes from oxidative stress and damage caused by I/R.

While NO is a relaxing factor in the endothelium and serves as a radical scavenger, in the presence of superoxide during oxidative stress, NO forms $ONOO^-$ which can cause damage in the myocardium [4, 35, 36]. It was previously reported that oxidative stress was a significant source of NO during I/R, as well as that NO synthesis in the cardiomyocytes was associated with the induction of high output NOS. The level of $(NO_x)^-$ in cardiac cells was also increased due to I/R [14]. Likewise, in the present study, there was an increased expression of iNOS and intensified production of $(NO_x)^-$ during I/R. The expression of iNOS and $(NO_x)^-$ level positively correlated with the cell injury, NOX2 and NOX4 levels, and with ROS/RNS level, confirming the conception of overproduction of ROS, disrupted NOS expression, and increased production of nitrate/nitrite due to I/R. Recent works on I/R-injured rat hearts proved that the pharmacological regulation of NOS expression and NO bioavailability attenuated cardiac injury and improved the heart's mechanical function [3, 37–39]. In the current investigation, the Klotho protein decreased the expression of iNOS, reduced the production of NO, thus contributing to the protection against nitrosative stress. Interestingly, Klotho deficiency has been linked to the disrupted expression of iNOS in the cardiomyocytes [40]. Regulated NO synthesis in the vascular endothelial cells and improved endothelial function during Klotho overexpression were observed as well [41, 42]. Similarly, Klotho reduced iNOS expression and attenuated NO overproduction in HUVECs or pancreatic beta-cells during stress conditions [43, 44]. The research showed that supplementation of cardiomyocytes with Klotho during I/R, regulated the production of $(NO_x)^-$ to the level observed in the aerobic control group. Thus, Klotho can be recognised as a potential factor that supports the reduction of nitrosative stress in the heart during I/R.

The studies showed that a switch from lactate uptake to lactate production occurs in the heart during myocardial ischemia [8, 9]. Importantly, an overproduction and accumulation of lactate have been implicated as a factor that causes cellular

damage during ischemia directly or indirectly [45]. It was previously reported that administration of the Klotho protein supported the viability and recovery of a proper metabolism in I/R-injured cells [7]. In this study, I/R injury led to reduced glucose uptake and increased production of lactate in the cardiomyocytes, confirming unbalanced cellular metabolism. The glucose uptake negatively correlated with the magnitude of injury, indicating disrupted metabolic functions. Importantly, it was reported that an intensified glycolysis is mainly caused by increased net glycogen breakdown rather than high glucose uptake [8, 9]. The cardiomyocytes under long-time hypoxia showed suppression of cellular glucose metabolism as well [46]. In the current study, the production of lactate positively correlated with cell injury and oxidative/ /nitrosative stress, confirming the mechanism of metabolic disruption during I/R. Administration of the Klotho protein regulated the glucose uptake to the level observed in the aerobic control group and limited subsequent production of lactate in the cardiomyocytes subjected to I/R. Interestingly, increased expression of the GLUT1 glucose transporter, as well as the enhanced glucose uptake and metabolism that followed, prevented apoptosis and the development of heart failure in response to hypoxia or pressure overload in animal models [47–49]. Klotho deficiency led to insulin resistance in the murine skeletal muscle, whereas Klotho overexpression increased glucose-induced insulin secretion in MIN6 beta-cells [50, 51]. It was found that the fibroblast growth factor (FGF) 21 stimulates glucose uptake in adipocytes by the induction of glucose transporters. Since Klotho is a co-receptor for FGF, it could be implicated in the glucose transportation and metabolic homeostasis through FGF/FGF receptor/Klotho signalling pathway [52]. Herein, it is reported that the Klotho protein supported glucose uptake and metabolic activity in cardiomyocytes during I/R injury.

Conclusions

The present research showed that the administration of Klotho during I/R injury contributed to: a) ameliorated cell damage; b) reduced oxidative and nitrosative stress; c) regulated glucose uptake and lactate production in the cardiomyocytes, and therefore, d) Klotho may be considered cardioprotective.

Further research is required to reveal the precise molecular mechanism by which Klotho could be involved in oxidative/nitrosative stress inhibition and glucose uptake recovery in cardiomyocytes during I/R.

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REVIEW ARTICLE

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Post-percutaneous coronary intervention angina: From physiopathological mechanisms to individualized treatment

Leonardo De Luca[1], Giuseppe M.C. Rosano[2], Ilaria Spoletini[2]

[1]Department of Cardiosciences, A.O. San Camillo Forlanini, Rome, Italy
[2]Center for Clinical and Basic Research, Department of Medical Sciences, IRCCS San Raffaele Pisana, Rome, Italy

Abstract

Chronic ischemic heart disease (IHD) is a multifactorial disease with different underlying pathogenetic mechanisms. Percutaneous coronary intervention (PCI) is widely used in patients with IHD in order to reduce angina recurrence. However, after complete or incomplete revascularization procedures, patients may still present anginal symptoms, with a detrimental impact on quality of life and prognosis.

This review summarizes the pathogenic mechanisms and the main challenges encountered in the diagnosis and management of post-PCI angina. (Cardiol J 2022; 29, 5: 850–857)

Key words: angina, ischemic heart disease, percutaneous coronary intervention, medical therapy, quality of life

Introduction

Ischemic heart disease (IHD) is the leading cause of death and disability for both sexes and its prevalence increases in an ageing population [1, 2]. The most frequent, and often the first manifestation of IHD, is chronic stable angina that affects approximately 112 million people worldwide [3, 4]. Besides pharmacological treatment, percutaneous coronary intervention (PCI) is widely used worldwide in IHD patients in order to reduce angina recurrence. However, up to 30% of IHD patients with stable angina continue experiencing symptoms despite treatment and revascularization procedures [5, 6].

Many post-PCI patients are burdened with recurrence of angina, impaired exercise capacity and quality of life. In fact, angina prevails over myocardial infarction (MI) and heart failure as a reason for impaired quality of life and disability [7]. Greater symptoms of physical limitation are strongly predictive of secondary events and poorer survival, independently of other factors [7].

Finally, a common phenomenon is represented by readmissions following PCI. Indeed, approximately 25% of patients have unplanned readmissions within 6 months [8]. This is due to several factors, 44% of which are cardiac reasons [8]. Interestingly, angina and coronary artery disease (CAD) are the biggest contributors to the readmissions due to cardiac reasons within 30 days and 1 year after the index PCI [8]. Readmissions after PCI may be considered as an adverse outcome for the patient and an unnecessary cost for the healthcare system.

Taking into account all these issues, the present reviews summarize the physiopathological mechanisms and the main challenges faced by patients with post-PCI angina, with a main focus on relapses of angina symptoms, choice of treatment and its optimization.

Address for correspondence: Leonardo De Luca, MD, PhD, FACC, FESC, Department of Cardiosciences; Division of Cardiology, A.O. San Camillo Forlanini, Circonvallazione Gianicolense, 87, 00152 Roma, Italy, tel: +39-06-58704419, e-mail: leo.deluca@libero.it; ldeluca@scamilloforlanini.rm.it

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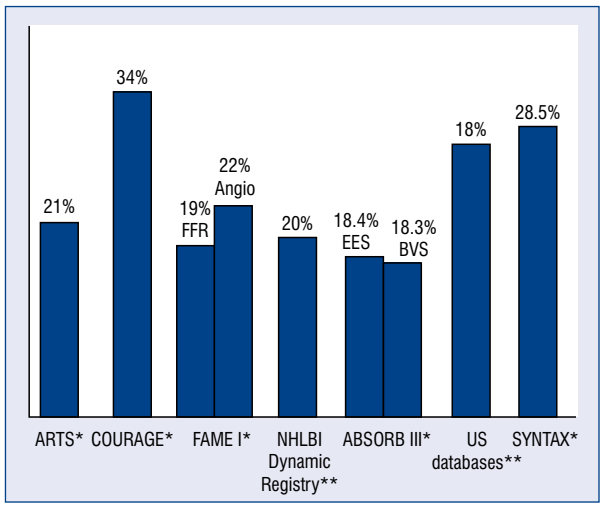

Figure 1. Incidence of recurrent post-percutaneous coronary intervention angina according to main randomized clinical trials (*) and registries (**); BVS — bioresorbable vascular scaffold; EES — everolimus--eluting stent; FFR — fractional flow reserve.

Recurrence of ischemia and angina in post-PCI patients

Figure 1 shows the incidence of angina recurrence after PCI in recent randomized clinical trials and international registries. In a study including more than 1000 stable angina patients evaluated with an exercise test after successful planned PCI, 29% still had an abnormal result at 1 month, which reached 31% of cases at 6 months [9]. Accordingly, meta-analyses of studies and registries in post-PCI patients demonstrated that, within 1 year after successful PCI, the recurrence of angina ranges between 20% and 30% [10] and, within 3 years, angina persisted or reoccurred in up to 40% of cases, leading to higher healthcare costs [11]. Of note, a real-world analysis [11] on the clinical and economic burden associated with post-PCI angina recurrence found that total healthcare costs in the first year after the index PCI were 1.8 times greater for those with angina or chest pain compared to angina-free patients.

Mechanisms underlying post-PCI angina recurrence are multiple and may include non-cardiovascular, cardiovascular non-coronary and coronary causes (Fig. 2). These latter may be functional and structural.

Functional mechanisms

Nowadays, functional reasons prevail over the structural ones and microvascular dysfunction is found in 64% of angina patients, in the absence of obstructive functionally significant epicardial

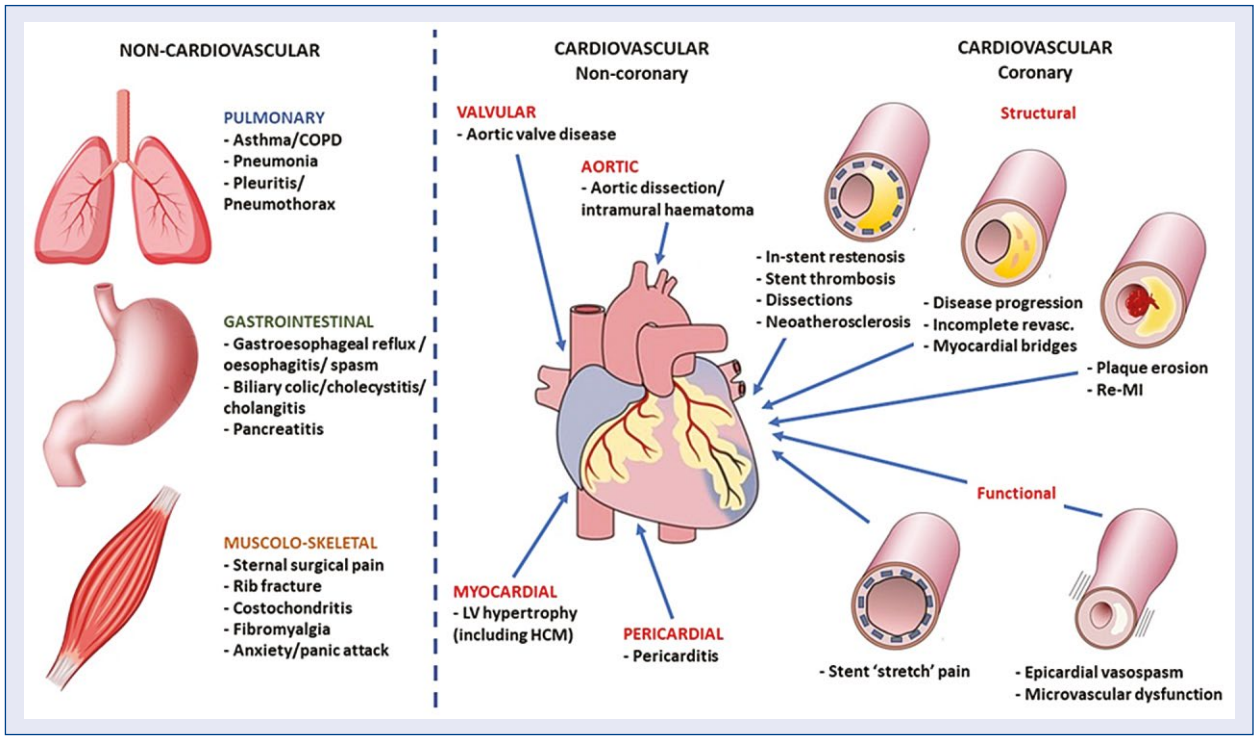

Figure 2. Cardiovascular and non-cardiovascular mechanisms of post-percutaneous coronary intervention angina recurrence; COPD — chronic obstructive pulmonary disease; HCM — hypertrophic cardiomyopathy; LV — left ventricle; MI — myocardial infarction.

stenosis, with a slightly superior prevalence of female sex [12]. Coronary artery vasospasm is also prevalent and is associated with silent myocardial ischemia, effort-induced angina and MI [12]. Similarly, myocardial bridging, a congenital anomaly in which a segment of a coronary artery presents an intramuscular course under a "bridge" of overlying myocardium, may cause vessel compression in systole, resulting in hemodynamic changes that may be associated with myocardial ischemia and angina [11].

Unfortunately, there is a paucity of data on the rate of functional reasons for ischemia along with epicardial stenosis due to an obsolete view that epicardial stenosis was the main reason for ischemia and angina. Last but not least, another key pathophysiological mechanism underlying symptoms and signs of myocardial ischemia, either in the presence or in the absence of an obstructive stenosis, is represented by myocardial cellular metabolic disturbances. The latter may cause ischemia and angina, even after removal of significant stenosis, further highlighting the need of a paradigm shift in stable IHD [13].

For all of these reasons, a functional evaluation is pivotal in PCI patients. There is evidence that a functional evaluation of coronary vasculature during PCI is feasible and improves a post-PCI drug treatment approach, patients' symptoms and quality of life [14]. As demonstrated by the Fractional flow reserve versus Angiography for Multivessel Evaluation (FAME 2) trial [15], routine measurement of fractional flow reserve in patients with multivessel CAD who are undergoing PCI with drug-eluting stents significantly reduced the rate of the composite endpoint of death, nonfatal MI, and repeat revascularization at 1 year. Due to its long-term safety, fractional flow reserve guidance of multivessel PCI should be the standard of care, as also elucidated by the FAME 1 [16].

Structural mechanisms

Structural causes of post-PCI angina include in-stent restenosis, stent thrombosis, progression of atherosclerotic disease in other coronary segments and incomplete revascularization. The incidence of stent thrombosis and in-stent restenosis, the two major causes of stent failure, has considerably been reduced in recent years by the introduction of new-generation drug-eluting stents [17]. Finally, it was investigated as to whether the type of stent influences frequency of angina after PCI. One study found no significant association between stent type and angina at 1 year after PCI [18]. Similarly, the A BioreSORBable vascular scaffold versus drug-eluting stent in coronary disease (ABSORB) III trial [19] found no differences in adverse events at 1 year in CAD patients treated with an everolimus-eluting bioresorbable vascular scaffold, as compared with an everolimus-eluting cobalt-chromium stent.

Recurrence of angina due to the progression of coronary atherosclerosis in coronary segments different from those treated with PCI, it is also infrequent in the months after the procedure (only 5% of major adverse events were related to non-culprit lesions in the Providing Regional Observations to Study Predictors of Events in the Coronary Tree [PROSPECT] study at 1 year follow up [20]), even though it accounts for approximately half of recurrent coronary events. A more common scenario is currently represented by incomplete coronary artery revascularization (IR), with incidence rates ranging from 17% to 85% in post-PCI patients [21, 22]. Such a huge variability is due to differences in study definitions of IR as well in the methodology used to analyse its frequency [23]. Regardless the type of revascularization, IR significantly impacts patient prognosis, increasing the risk of death, MI, repeated revascularization, adverse events and lifestyle-limiting angina [23]. Predictors of IR are older age, presence of multiple comorbidities, complex coronary lesions, hyperlipidemia, total occlusion and number of diseased vessels [23]. As such, IR is considered a marker of complexity that allows the identification of high-risk patients in whom medical therapy is therefore pivotal [24]. Of note, the Ranolazine in patients with Incomplete reVascularisation after Percutaneous Coronary Intervention (RIVER-PCI) study [25] aimed to prove the efficacy of ranolazine in about 2500 patients with IR after PCI. Although this trial confirmed that ischemia-driven events in patients with angina and incomplete revascularization following PCI are common (27% over 1.8 years), it failed to prove prognostic benefits of the drug in this population [25]. However, there were significant improvements in the frequency of angina following PCI in both arms, with no differences between ranolazine vs. placebo at 1 month (86.6 vs. 85.8, $p = 0.62$) or 12 months (88.4 vs. 88.5, $p = 0.6$). Patients with diabetes appeared to have a benefit with ranolazine for angina frequency at 6 months (88.3 vs. 85.4, $p = 0.033$; p for interaction $= 0.02$). This difference, however, dissipated by 12 months ($p = 0.18$). Notably, this trial had important limitations since it included a mixed group of patients with IR, including untreated chronic total

occlusions and diffuse distal disease. In addition, the functional significance of untreated CAD was not routinely assessed.

Heart rate control in post-PCI angina patients

Another key issue in post-PCI angina patients is poor control of heart rate (HR). It is well-known that resting HR has an important prognostic role [26], since it independently predicts total and cardiovascular mortality in angina patients. Even among patients treated with PCI, HR at discharge is a strong predictor of mortality [27]. As such, HR is a component of both ischemic and bleeding risk scores. This is due to the role of HR in atherogenesis, atherosclerotic plaque formation and progression, and vascular remodeling [28]. Further, HR acts as a trigger of ischemia in patients with CAD [29]. Conversely, HR reduction leads to clinical benefits and, for this reason, lowering HR is a therapeutic target for angina [30].

The latest 2019 European Society of Cardiology guidelines for the management of chronic coronary syndromes (CCS) [2] continue recommending target levels of resting HR between 55 and 60 bpm. Unfortunately, the latest registries on CCS suggest poor control of resting HR in this population. For instance, in the prospeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease (CLARIFY) registry [31], including more than 32,000 stable angina patients, 50% of the symptomatic angina patients had resting HR above 70 bpm, in spite of the beta-blocker therapy, which was taken by 75% of the patients. In the same registry, HR above 70 bpm was associated with higher prevalence and severity of angina.

Choice of anti-anginal drugs/ /individualized treatment

Due to the multifactorial origin of IHD, in which different pathogenetic mechanisms may co-exist, leading to different clinical pictures with different predominances of symptoms over time [32], it is now been ascertained that patients need several anti-angina drugs in order to control symptoms, following a patient-oriented approach (Fig. 3). The choice of treatment should be related to the mechanisms causing angina, co-morbidities, potential drug-interactions and tolerability. Thus, an individualized approach to angina treatment, the "Diamond" approach, which takes into consideration all these factors, has been proposed (Fig. 4) [32].

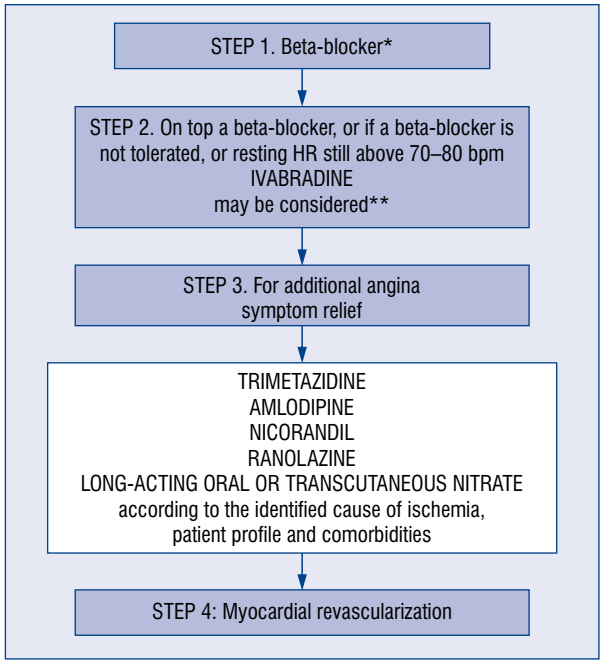

Figure 3. Flowchart of stable angina pectoris treatment; HR — heart rate.

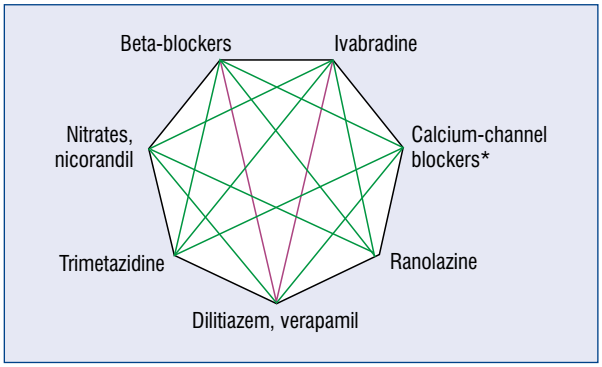

Figure 4. Combinations among classes of antianginal drugs according to the Diamond approach; *dihydropyridines.

In particular, current first line anti-anginals, beta-blockers and calcium-channel blockers have not proven to have prognostic benefits (except for patients within 1 year after MI), as demonstrated by the CLARIFY study [33]. Further, recent meta-analyses found no evidence of superiority of one anti-angina class over another in reducing ischemia and angina [34].

The latest CCS guidelines [2] also acknowledged the lack of evidence of superiority amongst the various anti-angina classes, and despite whether the line categorization is kept, they confirmed

the need of a patient tailored approach, endorsing the early use of the so called "second line drugs" along with the "first line drugs", in order to provide adequate treatment according to the individual characteristics of the patient.

For all these reasons, more recent drugs with proven additional anti-anginal efficacy should be considered earlier in post-PCI symptomatic patients, along with the so called "first-line" anti-anginal drugs, given that the categorization of an antianginal drug of first or second line is not confirmed [35]. Thus, ivabradine, trimetazidine and ranolazine should be considered, as described elsewhere [32].

Briefly, ivabradine was found to reduce symptoms and improve quality of life in a post-hoc analysis on angina patients with a history of revascularization, who remained symptomatic in spite of an individually optimized dose of a beta-blocker [36]. A recent study [37] in patients with residual ischemia after PCI, demonstrated ivabradine benefits on significant reduction of HR, lower incidence of angina during the stress test and improvements in functional capacity.

As for trimetazidine, it has proven benefits in patients with recurrent angina after PCI in spite of beta-blocker therapy such as preventing recurrence of angina, reducing restenosis, with a good safety profile [38].

Yet, it should be noted that some of these studies are single-center or open-label. The efficAcy and safety of Trimetazidine in patients with angina pectoris having been treated by Percutaneous Coronary Intervention (ATPCI) trial [39], was a randomized, multicenter, placebo controlled trial on more than 6000 post-PCI patients, which failed to demonstrate significant benefits of trimetazidine vs. placebo on the primary efficacy endpoint, a composite of cardiac death, hospital admission for a cardiac event, recurrence or persistence of angina requiring other antianginal drugs or recurrence or persistence of angina requiring a coronary angiography. However, it is important to underline that the ATPCI study was not designed to evaluate antianginal properties of trimetazidine since patients included were asymptomatic and at low risk [39].

Optimization of anti-angina therapy

Despite its importance, anti-anginal therapy is still often neglected in post-PCI angina patients. In the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial [40], only 60% of the patients were on optimized medical therapy after PCI. In the Suivi d'une cohorte de patients COROnariens stables en région NORd-Pas-de-Calais (CORONOR) registry [41], the average number of anti-anginal drugs in post-PCI patients was rather low (mean: 1,4). In the recent International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial [42], optimal medical therapy was prescribed, and risk factors control was obtained in more than 5000 patients with moderate to severe ischemia. The results demonstrated no superiority of PCI as an initial strategy on top of optimized medical therapy over optimized medical therapy alone. However, in the overall trial population, which included 35% of participants without angina at baseline, patients randomly assigned to the invasive strategy had greater improvement in angina-related health status than those assigned to the conservative strategy. The modest mean differences favoring the invasive strategy in the overall group reflected minimal differences among asymptomatic patients and larger differences among patients who had had angina at baseline [43].

It is even more striking that, in a study following post primary PCI patients [44], among the 30% who reported angina within 6 weeks after the procedure, 68% remained treated only with beta-blocker, and did not receive a second anti-anginal drug.

Another main issue observed in clinical practice is the de-escalation of antianginal medications after PCI. There is evidence that down-titration is associated with an increased risk of angina recurrence and worsening of health status, particularly among patients with incomplete revascularization [23]. Interestingly, in the aforementioned RIVER-PCI study [25], 67% of the patients were taking 0–1 anti-ischemic/angina drug in spite of the incomplete revascularization in parallel with the 44% reporting daily or weekly angina after the procedure.

The STable Coronary Artery Diseases RegisTry (START) study [45], a prospective, observational, nationwide study aimed to evaluate the presentation, management, treatment and quality of life of patients with stable CAD, revealed that treatment is still suboptimal in patients with angina. Although angina patients more frequently received antianginal drugs compared to patients without angina, the combinations of angina relief drugs were rarely employed.

Such an inadequate post-PCI anti-angina treatment could be due to different reasons. First, from a socio-psychological point of view, the desire of

both healthcare professionals and patients to believe that the problem is solved may lead to some kind of inertia. Second, there are reasons linked to the healthcare system, such as the lack of systematic monitoring of symptoms after PCI. A German study [46] demonstrated that 10% of ambulatory cardiologists did not ask patients about symptoms after PCI and 19% did not consider initiating drug therapy in angina patients with overruled significant coronary stenosis.

Third, a discrepancy between patient and doctor perceptions of burden of the disease may very often lead to under-recognition of angina. Up to 60% of the angina cases are not recognized by physicians in ambulatory practice, leading to lower rate of angina treatment up-titration [47].

A recent multinational European physician survey [48], on 659 general practitioners and cardiologists evaluating more than 1900 stable angina patients, found a striking underestimation of the disease burden, especially in elderly, women, and those patients with a long-standing diagnosis (more than 2 years). Moreover, patients who previously had a PCI had more severe stable angina, despite more intense medical treatment, than patients without previous PCI.

All these data demonstrate that close monitoring of stable angina patients and optimization of anti-angina therapy, even after a successful PCI, is mandatory in order to adequately treat symptoms and alleviate the disease burden.

Conclusions

Recurrence of angina is a frequent and still neglected condition after contemporary PCI. History of symptoms, clinical examination and functional imaging are essential to guide healthcare professionals in the search for possible underlying reasons for angina persistence and relapses in post-PCI patients. Optimizing anti-angina therapy is a necessary step, especially in absence of regional wall motion abnormalities.

Thus, an efficacious and repeated monitoring may help improve post-PCI management in clinical practice and, also, may prevent an excessive and unnecessary use of PCI before optimizing medical therapy.

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Does kidney function matter in pulmonary thromboembolism management?

Magdalena Pływaczewska, Piotr Pruszczyk, Maciej Kostrubiec

Department of Internal Medicine and Cardiology, Medical University of Warsaw, Poland

Abstract

Cardiovascular circulation and kidney function are closely interrelated. The impairment of renal function is a well-known hazard of increased mortality and morbidity of patients with heart failure or coronary artery disease. Acute pulmonary embolism (APE) impacts pulmonary and systemic circulation, and can severely impair functions of other organs, including kidneys, as a result of hypoxemia and increased venous pressure.

Previous studies indicate that renal dysfunction predicts short- and long-term outcomes and can improve the risk assessment in APE. However, renal function should also be cautiously considered during the diagnostic workup because the contrast-induced nephropathy after computed tomography pulmonary angiography is noticed more frequently in APE. Chronic thromboembolic pulmonary hypertension (CTEPH) is a rare but imminent complication of APE. This condition promotes renal impairment by increasing venous pressure and decreasing glomerular filtration. The renal function improvement and serum creatinine concentration reduction were noted in CTEPH subgroup with glomerular filtration rate ≤ 60 mL/min/1.73 m^2 after successful treatment.

In this review, we present the essential research results on the kidney function in thromboembolism disease. (Cardiol J 2022; 29, 5: 858–865)

Key words: renal dysfunction, contrast-induced nephropathy, pulmonary embolism, chronic thromboembolic pulmonary hypertension, prognosis, mortality

Introduction

Cardiovascular diseases are the most frequent causes of morbidity and mortality in the general population, and impaired renal function is a broadly known risk factor increasing mortality [1]. The association between kidney function and diseases of heart and vessels seems to be obvious. Approximately 4.5% of the general population has a glomerular filtration rate (GFR) < 60 mL/min [2], which puts them at risk.

To assess renal function, serum plasma creatinine and GFR are the most widely used. However, the direct measurement of GFR is usually avoided, and its estimations based on the modification of Diet in Renal Disease (MDRD) [3] and the Cockcroft-Gault (C–G) formula [4] are convenient and accurate substitutes.

Acute pulmonary embolism (APE) does not only have an impact on pulmonary but also systemic circulation and can impair functions of other organs causing hypoxemia and increased venous pressure. It should be underlined that kidneys are susceptible to hypoxemia [5]. The previous studies indicate that renal dysfunction predicts short- and long-term outcomes and can improve the risk assessment in APE [6, 7]. However, kidney function and its assessment are essential in various thromboembolic disease.

At diagnosis

In patients with high clinical probability and abnormal D-dimer levels, computed tomography pulmonary angiography (CTPA) is performed not only to confirm the diagnosis of APE but also to ob-

Address for correspondence: Magdalena Pływaczewska, MD, Department of Internal Medicine and Cardiology, Medical University of Warsaw, ul. Lindleya 4, 02–005 Warszawa, Poland, tel: +48 517930273, e-mail: ma.plywaczewska@gmail.com

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tain information about possible right ventricle (RV) dysfunction [8]. Nevertheless, CTPA can trigger contrast-induced acute kidney injury (CI-AKI) [9], which is usually defined as an increase of creatinine level ≥ 0.5 mg/dL or > 25% from baseline within 48 hours of contrast usage [10]. Some studies have suggested that APE patients are more vulnerable to, and more frequently experience, CI-AKI. Firstly APE is a condition leading to impairment of renal function. As a consequence of thrombi closure and vasoconstriction of the pulmonary arteries, pulmonary resistance rises, and subsequently the pressure in the RV also increases. Hemodynamic destabilization of the RV effects a reduction in left ventricular load and, consequently, a reduction in stroke volume and systemic hypotension [11]. Because the RV is not adapted to sudden pressure overloads, its failure occurs, which results in congestion in the peripheral circulation. The increase of a central venous pressure leads to a stagnation of blood in central veins and subsequent passive hyperemia of liver and kidneys [12]. Elevated central venous pressure, hypoxemia and decreased cardiac output results in organ hypoperfusion [13] and can be a factor in renal dysfunction [14]. Coexisting hypoxemia is a result of pulmonary circulatory failure and leads to ischemic damage [15]. Kidneys are among the most sensitive organs to hypoxemia [5]. Increased venous pressure causes a reduction of trans-glomerular pressure gradients and impairs kidney perfusion. This mechanism also activates the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system leading to oxygenic stress and further renal function impairment.

Moreover, as a consequence of respiratory failure, a lower level of pH and bicarbonate is observed in arterial blood. This state promotes the production of reactive oxygen species, which aggravate already present ischemic damage. One of the suspected mechanisms of CI-AKI is also an ischemic injury of the renal medulla and production of reactive oxygen species, which damage tubules and endothelium [16]. We can conclude that all of APE's pathophysiological consequences promote kidney dysfunction and the occurrence of CI-AKI.

Kooiman et al. [17], in a group of 237 patients with suspicion of pulmonary embolism, studied the frequency and risk factors of contrast-induced nephropathy (CIN) after CTPA. The prevalence of CIN was 8.9%. Independent predictors of impaired renal function after contrast administration were age over 75 years, diabetes mellitus, non-steroidal anti-inflammatory drug use, and multiple myeloma. Doganay et al. [18], in a retrospective study of 122 patients with confirmed APE, showed that the incidence of CI-AKI is more frequent in APE than in other conditions examined with contrast-enhanced computed tomography, 13% vs. 3–4%, respectively. The logistic regression analysis confirmed lower pH in arterial blood gas and older age as the risk factors of CI-AKI. Other remarkable hazards were chronic heart failure, higher pressure in pulmonary artery estimated in transthoracic echocardiography, administration of angiotensin converting enzyme inhibitors (ACE-I) or angiotensin receptor blocker (ARB), and low HCO_3^-. Some of these factors, like age, chronic heart failure, and treatment with ACE-I or ARB, can be found in the risk score scale created by Mehran et al. [19] for patients after a coronary intervention. However, additional hazards are more frequent in patients with APE, especially high and moderate-high risk class according to the European Society of Cardiology (ESC) [8]. Summarizing, there is a remarkable overlap of the risk factors between the CIN risk score [19] and the APE risk score [20]. Consequently, Ho and Harahsheh [21] created the study comparing CIN risk score and pulmonary embolism severity index (PESI) in the prediction of renal insufficiency in critically ill patients suspected on APE. They included 137 intensive care unit (ICU) patients without end-stage renal failure. The study revealed that CIN risk score was significantly better than PESI in the prediction of CIN leading to dialysis (area under curve [AUC] 0.864, 95% confidence interval [CI] 0.795–0.916 vs. 0.731, 95% CI 0.649–0.804; $p = 0.001$, respectively). However, PESI had the advantage of better survival prognosis (AUC 0.794, 95% CI 0.716–0.858 vs. 0.625, 95% CI 0.538–0.706; $p = 0.001$). The authors suggested that in critically ill patients with suspicion of APE and high risk of CIN, other diagnostic methods should be considered instead of CTPA. Michell et al. [22] showed that after CTPA the frequency of CIN is higher than after other contrast procedures, at 14% vs. 10%, respectively.

Additionally, the prevalence of CIN was related to increased risk of poor outcome, such as severe renal failure and death (16% of patients with CIN after CTPA). The guidelines of the Contrast Medium Safety Committee 2018 [23] recommend hydration (saline or sodium bicarbonate) to prevent CI-AKI in patients at risk of this complication. In a randomized control trial, Turedi et al. [24] compared the prophylaxis of CIN after CTPA with N-acetylcysteine, sodium bicarbonate and saline. In the group of 231 patients, 15.2% (32/231) had CIN, but none of the prophylaxes was more effective. The multivariate logistic regression analysis

indicated that only basal GFR and the presence of hypotension were independent predictors of CIN development. Kooiman et al. [25] compared a lack of hydration with hydration of 250 mL 1.4% sodium bicarbonate in the prophylaxis of CI-AKI after CTPA in 138 patients with chronic kidney disease (CKD) and suspicion of APE. They did not observe differences in the frequency of CI-AKI between groups, and suggested that not using pre-hydration would avoid a delay in performing CTPA and proper diagnosis. Another interesting study is the recent Kompas Randomized Clinical Trial [26]. In a group of 523 patients with stage 3 of CKD, who underwent contrast-enhanced computed tomography, no hydration was compared with sodium bicarbonate administration. The CI-AKI occurred in 11 (2.1%) patients. In the no pre-hydration group it was 7 of 262 (2.7%), and 4 of 261 (1.5%) in the pre-hydration group and the relative risk was 1.7 (95% CI 0.5–5.9; p = 0.36). The authors concluded that withholding hydration is safe and cost-effective.

During hospitalization and after discharge

The risk stratification of pulmonary embolism patients is crucial in the selection of medical management. As previously mentioned, APE impairs not only pulmonary circulation but also the systemic circulation and function of many organs, including kidneys, the dysfunction of which may negatively influence the outcome.

In the ICOPER study, creatinine > 177 μmol/L predicted 3-month mortality [27]. The authors of the Hestia study indicated that the diagnosis of APE in patients with creatine clearance < 30 mL/min (C–G) should be the premise for in-hospital treatment [28]. The studies conducted in our department revealed that renal dysfunction predicted short and long-term outcome and could be useful in improving the risk assessment in APE [6]. In a group of 2247 APE patients hospitalized in three European centers, GFR ≤ 60 mL/min/1.73 m^2 calculated by MDRD was a risk factor of mortality during 30- and 180-day observation. Moreover, the inclusion of GFR ≤ 60 mL/min/1.73 m^2 enhanced the ESC risk stratification model, with a net reclassification index (NRI) of 0.42. The impaired kidney function, assessed as a drop in eGFR, was also linked with a higher occurrence of bleeding (odds ratio [OR] 0.90 per 10 mL/min/1.73 m^2, 95% CI 0.85–0.95; p = 0.0002). The analysis of the same group of patients showed no significant difference in mortality prediction between the two GFR estimation formulas: C–G vs. MDRD. The areas under the receiver operating characteristics curves for both the methods were similar [29].

The comparison of various methods of GFR estimation (C–G vs. CKD-EPI) was recently performed on data from the RIETE registry [30]. Among the 4676 patients with GFR ≤ 30 mL/min according to at least one of the formulas, these result was not confirmed in 40.7% individuals by the other equation. However, patients with a diagnosis of severe renal impairment, regardless of the method used for GFR calculation, had a higher rate of major bleedings during anticoagulation treatment (approximately 10% vs. 4%). In the subgroups with low GFR the all-cause mortality rates were higher than in patients without severe renal failure.

In another single-center study eGFR ≤ 35 mL/min in normotensive APE patients was associated with higher risk of 30-day mortality and, when combined with the troponin level, also improved risk stratification [7]. Similarly, Altinsoy et al. [31] in a multivariate analysis demonstrated that GFR estimated by CKD-EPI or MDRD coexisting with an elevated troponin concentration were independent predictors of an adverse outcome in normotensive patients with APE. In this study, the GFR also correlated with RV dysfunction.

Serum creatine measurement is variable and reflects somewhat the functional changes of glomerular filtration roughly mirroring kidney injury [32]. New markers surpass serum creatinine in assessing renal filtration as well as glomerular or tubulointerstitial damage. Because of the early occurrence of novel renal markers, the diagnosis of kidney dysfunction might be suspected before any change in creatinine concentration. Neutrophil gelatinase-associated lipocalin (NGAL) [33] and cystatin C are examples of these compounds [34]. A study of APE patients showed that NGAL plasma levels were significantly higher in non-survivors [35]. Furthermore, increased levels of NGAL and cystatin C in patients with APE were associated with higher 30-day all-cause, pulmonary embolism-related, and 180-day mortality. The elevation of NGAL in a group with low risk of death due to APE had 100% negative predictive value for 30-day all-cause death. Plasma concentration of cystatin C was the most significant predictor of death in multivariable analysis. Even though novel biomarkers seem to be more precise than those based on serum creatinine GFR, they are rarely available and are not commonly used (Table 1).

Table 1. Overview of important studies on renal function impairment in acute pulmonary embolism (APE).

Study or author's name	Year	Patients group	Main results
ICOPER study [27]	1999	2454	Creatinine > 177 μmol/L predicts 3-month mortality
Kostrubiec el al. [7]	2010	220	eGFR ≤ 35 mL/min in normotensive APE patients increases the risk of 30-day mortality eGFR combined with troponin level — improves the risk stratification
Kostriubiec et al. [35]	2012	142	NGAL plasma level was significantly higher in non-survivors Increase level of NGAL and cystatin C — higher rate of 30-day all-cause and pulmonary embolism-related mortality, and 180-day mortality Cystatin C — most significant predictor of death in multivariable analysis
Hestia study [28]	2013	496	APE patients with eGFR < 30 mL/min (C-G) as an indicator of in-hospital treatment
Altınsoy et al. [31]	2017	99	GFR (CKD-EPI or MDRD) with elevated troponin is an independent predictor of adverse outcome in normotensive APE GFR correlated with right ventricle dysfunction
Ho and Harahsheh [21]	2018	137	CIN risk score is significantly better than PESI in the prediction of CIN leading to dialysis PESI has the advantage of better survival prognosis
Kostrubiec et al. [6]	2019	2247	GFR ≤ 60 mL/min/1.73 m^2 (MDRD) is a risk factor of 30- and 180-day mortality GFR ≤ 60 mL/min/1.73 m^2 enhanced the European Society of Cardiology risk stratification Lower eGFR is associated with higher occurrence of bleeding
Catella et al [30] RIETE study sub-analysis	2019	4676	Severe renal impairment is associated with higher rate of major bleedings during anticoagulation Low GFR subgroups with higher all-cause mortality

CIN — contrast-induced nephropathy; CKD-EPI — Chronic Kidney Disease Epidemiology Collaboration; eGFR — estimated glomerular filtration rate; MDRD — modification of diet in renal disease; NGAL — urinary neutrophil gelatinase-associated lipocalin; PESI — pulmonary embolism severity index

Long-term follow-up after an APE episode

Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the subtypes of pulmonary hypertension (PH) [36]. The epidemiology of this disease is barely known. In a meta-analysis of 16 studies on CTEPH, its pooled incidence in unselected patients after APE during 2–3 years of follow-up was 0.56% [37]. Researchers observed that among survivors, the frequency of CTEPH was 3%. Clinical practice suggests that this morbidity rate may be more accurate. The CTEPH is considered to develop as a consequence of the impaired resolution of pulmonary thrombi, which subsequently become endothelized. This leads to chronic obstruction of the pulmonary arteries, high pulmonary vascular resistance, increased pressure in the pulmonary circulation, and progressive right heart failure [12]. In patients with CTEPH, impairment of kidney function also plays an important role. Chronic elevation of central venous pressure secondary to RV dysfunction runs to high renal venous pressure [38] and a drop in effective filtration pressure [39]. That process activates neurohormonal ways, including RAAS, and pro-inflammatory pathways, which further decline the filtration fraction [40]. The activation of the RAAS also leads to oxidative kidney injury [41, 42]. Additionally, PH worsens the course of CKD [43]. This is associated with a state of elevated catecholamine levels, activation of RAAS, and progressive RV dysfunction [44, 45]. The above cascade deteriorates PH. Summarizing, the impaired renal function may be a consequence of PH but also might be a reason for PH exacerbation [46]. Nevertheless, PH is associated with higher mortality in patients with CKD [47].

Chronic thromboembolic pulmonary hypertension is a complication of pulmonary embolism, with abysmal prognosis if left untreated [48]. The first-choice treatment is the surgical removal of

Table 2. Overview of important studies on renal function impairment in chronic thromboembolic pulmonary hypertension (CTEPH).

Study or author's name	Year	Patient group	Main results
Delcroix et al. (International Prospective Registry) [51]	2016	679 patients with CTEPH	Dialysis-dependent renal — risk factors of death
Darocha et al. [58]	2019	250 BPA in 41 patients	Low rate of CIN (0.8%) Renal function improvement and creatinine reduction after BPA treatment
Kriechbaum et al. [60]	2019	265 BPA in 51 patients	CI-AKI occurred after 6 (2.3%) BPA Patients with CKD — renal function improved after BPA
Kimura et al. [61]	2015	46 patients treated by BPA	Upturn of renal filtration in patients with initially impaired kidney function
Isobe et al. [62]	2019	45 patients	Increased of cardiac index and mixed venous oxygen saturation with a decrease of mPAP and PVR-predictors of renal insufficiency improvement after BPA

BPA — balloon pulmonary angioplasty; CI-AKI — contrast-induced acute kidney injury; CIN — contrast-induced nephropathy; CKD — chronic kidney disease; mPAP — mean pulmonary artery pressure; PVR — pulmonary vascular resistance

chronic thrombi from pulmonary arteries, i.e. endarterectomy (PEA) [49]. PEA is considered to be the optimal option but requires a cardiopulmonary bypass with deep hypothermia and total circulatory arrest [50]. The qualification for the procedure should be made by a highly specialized team. The decision depends on the patient's profile, comorbidities, and thrombi location [36]. The rate of operable vs. non-operable patients fluctuates 40–60% [51]. Successful treatment improves the prognosis and quality of life, and results in a better renal function [52]. According to the registry of 679 patients with CTEPH for the whole cohort, PEA was the strongest independent predictor of survival (HR 0.37; 95% CI 0.24–0.58; $p < 0.0001$) [51]. The analysis of preoperative characteristics of operated patients revealed dialysis-dependent renal failure as one of the risk factors of death (HR 11.52; 95% CI 1.42–93.48; $p = 0.0221$). Other independent risks factors of mortality for both the operated and the not-operated group were age, New York Heart Association class, right atrial pressure, history of cancer, left heart failure, and dialysis-dependent renal failure. However, it should be noted that 12–31% patients after PEA have persistent or recurrent PH [53, 54].

Balloon pulmonary angioplasty (BPA) is a feasible PEA alternative for patients with high perioperative risk, distal location of the lesion, or persistent PH [36, 54]. Subsequent percutaneous dilatation of occlusions and opening of obstructed pulmonary arteries improve the hemodynamic status, reduce symptoms, and lead to the decrease of cardiomarker levels [55]. Appropriate and multiple BPA results in the reduction of the pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (mPAP) [56, 57]. The optimal effect is usually achieved after 3–10 BPA sessions [48]. Every BPA session carries a considerable risk of contrast-induced nephropathy. However, Darocha et al. [58] described only 2 (0.8%) episodes of CIN following 250 BPA procedures in 41 patients, and no patient needed dialysis. Of interest, the renal function improvement and serum creatinine concentration reduction was noted in the CTEPH subgroup with GFR ≤ 60 mL/min/1.73 m^2 (12 patients, 29%) after BPA treatment. This was accompanied by a drop in mPAP, PVR, and N-terminal-pro-B-type natriuretic peptide and extension of the distance in the 6-minute walking test. The investigators noted that a relative increase of GFR, from the initiation of BPA therapy throughout the following 3–6 months after BPA, was correlated with relative changes of cardiac index, right atrial pressure, and mixed venous oxygen saturation. The study indicated that the incidence of CIN after BPA was a rare complication in comparison to percutaneous coronary intervention, despite the higher contrast volume. The rationale could be intravenous administration of contrast and better hemodynamic status of patients during BPA [59]. Higher frequency of CI-AKI was described by Kriechbaum et al. [60] in a group of 51 patients undergoing BPA. The AKI occurred after 6 (2.3%) procedures in 5 (9.8%) various patients following 265 BPA sessions. In all cases, AKI was stage I and no distinctive features for these patients from the rest of the study group were found. Analysis of the subgroup of patients with CKD revealed that renal function improved after BPA, which might be related to the improvement of the systemic circulation. Kimura et al. [61]

observed an upturn of renal filtration in patients with initially impaired kidney function in a group of 46 patients treated with BPA. Nevertheless, the rise of GFR was not significant for the entire study group. A recent study by Isobe et al. [62] indicated that some hemodynamic parameters, such as an increased cardiac index and mixed venous oxygen saturation with a decrease of mPAP and PVR, were predictors of renal insufficiency improvement in patients undergoing BPA. In conclusion, renal function may be significantly improved after successful sessions of BPA due to a drop in venous pressure, lower venous congestion in kidneys, and higher cardiac output (Table 2).

Chronic thromboembolic pulmonary hypertension is not the only type of PH affecting renal function. The coexistence of CKD and PH is obviously the most common in the most frequent type 2 PH, secondary to left heart disease [63]. The presence of PH in patients with renal insufficiency is associated with high all-cause mortality and frequency of cardiovascular events [64]. PH is a cause of the rapid progression of CKD [65]. Furthermore, CKD exaggerates PH [66].

Research on PH is developing quickly, increasing our understanding of its pathophysiology. Subsequent to this evolution, a recent paper by Simonneau [67] suggested a change of PH definition setting up the threshold of mPAP value at 20 mmHg instead of the previous 24 mmHg. According to this novel definition, to diagnose pre-capillary PH mPAP > 20 mmHg needs to be accompanied by pulmonary arterial wedge pressure ≤ 15 mmHg and PVR ≥ 3 Wood's units.

Conclusions

To conclude, kidney function is crucial for the proper management of pulmonary thromboembolism. Renal insufficiency increases the risk of CIN during the diagnostic process. CIN is observed in approximately 13% of patients undergoing CTPA due to pulmonary embolism suspicion. Both CKD and acute renal injury at pulmonary embolism diagnosis are markers of worse short- and long-term prognosis. The addition of the criterion: GFR below 60 mL/min, to sPESI can potentially improve risk stratification in APE. The impaired renal function can improve significantly after successful treatment of CTEPH.

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Mechanical circulatory support for high-risk percutaneous coronary interventions and cardiogenic shock: Rationale and design of the multicenter, investigator-initiated IMPELLA-PL registry

Arkadiusz Pietrasik[1], Aleksandra Gasecka[1], Marek Grygier[2], Tomasz Pawlowski[3], Jerzy Sacha[4, 5], Janusz Kochman[1]

[1]1st Chair and Department of Cardiology, Medical University of Warsaw, Poland
[2]Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland
[3]Department of Invasive Cardiology, Central Clinical Hospital of the Ministry of Interior and Administration, Warsaw, Poland
[4]Department of Cardiology, University Hospital in Opole, Poland
[5]Faculty of Physical Education and Physiotherapy, Opole University of Technology, Opole, Poland

Background

Despite tremendous progress in the pharmacotherapy and interventional treatment for coronary artery disease (CAD), CAD and its complications, including acute myocardial infarction (MI), remain the main cause of morbidity and mortality worldwide [1]. Patients undergoing high-risk percutaneous coronary intervention (PCI) and those with MI complicated by cardiogenic shock frequently require short-term mechanical circulatory support (MCS) [2, 3]. Traditionally, an intra-aortic balloon pump (IABP) was used to assist failing left ventricle (LV) in these clinical scenarios, as it was initially demonstrated to decrease all-cause mortality, compared with unsupported PCI [4]. However, the results of subsequent clinical trials showed conflicting results regarding the beneficial effect of IABP on long-term survival [5, 6], leaving percutaneous MCS and a scope of greatly unmet needs.

The Impella device (Abiomed, Danvers, MA, USA) is a microaxial, continuous blood flow pump and the smallest catheter-based LV assist device, which provides up to 5.0 L/min cardiac output [7]. In contrast to IABP, which creates a reverse blood flow to coronary arteries during diastole, providing a non-physiological MCS, Impella facilitates blood flow from the LV into the ascending aorta during systole, reducing LV preload and providing hemodynamic support in a physiological way [7]. Preliminary evidence from randomized clinical trials suggested the advantage of Impella devices over IABP, both in patients with MI complicated by cardiogenic shock and those undergoing high-risk PCI [8–10]. Despite conflicting results provided by recent systematic reviews and registry-based analyses [11–14], Impella devices have received a Class IIa recommendation (should be considered) in the recent European Society of Cardiology (ESC) guidelines for the treatment of acute heart failure patients [15]. Whereas ESC guidelines for myocardial revascularization did not provide clear recommendations regarding the use of Impella during high-risk PCI [2], the American College of Cardiology (ACC) granted a Class IIb recommendation for Impella prophylactic use during elective high-risk PCI procedures [16].

Following the approval of Impella for clinical use in Europe in 2005, it has been adopted world-

Address for correspondence: Arkadiusz Pietrasik, MD, PhD, 1st Chair and Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02–097 Warszawa, Poland, tel: +48 22 599 19 51, e-mail: arkadiusz.pietrasik@wum.edu.pl

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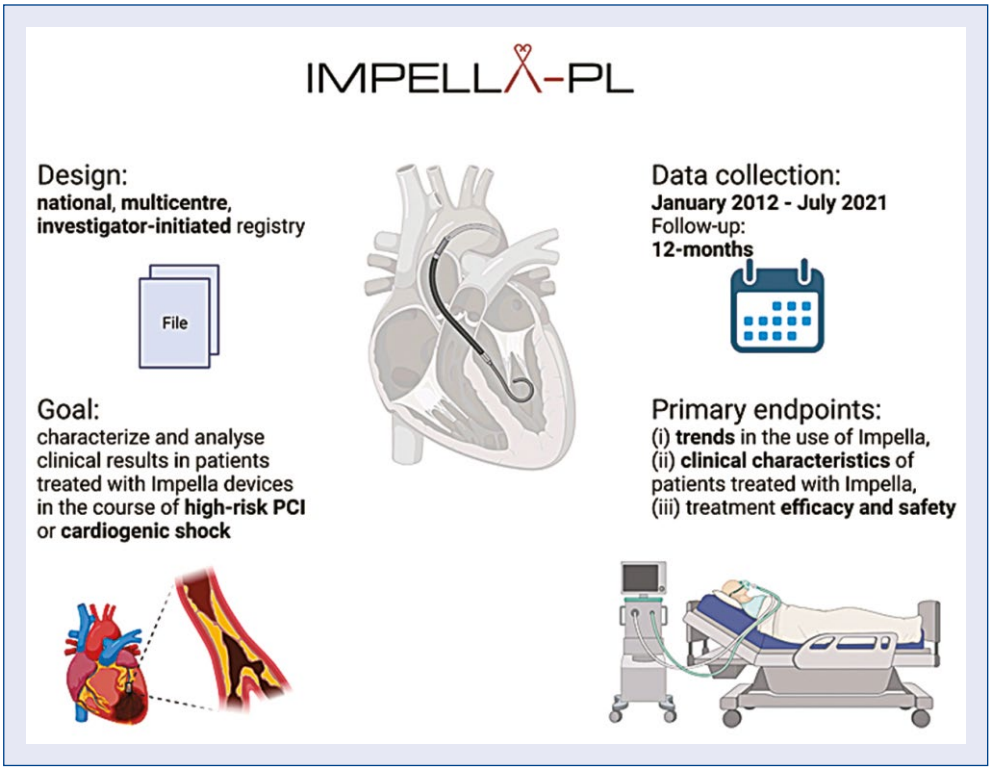

Figure 1. IMPELLA-PL registry scheme; PCI — percutaneous coronary intervention.

wide, with over 210,000 devices implanted up to date. Despite its widespread use, evidence-based data on the efficacy and safety of hemodynamic support with Impella in patients undergoing high-risk PCI and/or with cardiogenic shock are scarce. Therefore, the current landscape of Impella use is based on expert consensus, as acknowledged by recent position papers and consensus statements from various national societies [3, 17–20].

Since large randomized trials of hemodynamic support in patients undergoing high-risk PCI and with cardiogenic shock are challenging to conduct, few national registries have been launched which specifically focus on Impella devices: the Impella Italian (IMP-IT) Registry and German Impella Registry in Europe [21, 22] and the Catheter-Based Ventricular Assist Devices (cVAD) Registry in the United States (US) [23]. Considering various indications and types of Impella devices used in different countries and the lack of standardized algorithms for treatment qualification [19], it is crucial to establish new registries to further support decision making and form new recommendations in this challenging clinical scenario.

Regarding the growing complexity of percutaneous revascularization procedures in the recent decade, the use of the Impella devices have become a necessity in the interventional cardiology reference centres in Poland [24]. Careful monitoring of treatment with Impella, followed by analysis of the efficacy and safety of performed procedures are crucial to determine future directions of development for this emerging technology. To fill in this gap of knowledge, the IMPELLA-PL registry has been initiated.

Methods

Design

The IMPELLA-PL registry is a national, multicenter, investigator-initiated registry with the main objective to characterize the population of patients treated with Impella devices in the course of PCI and cardiogenic shock and to analyse the clinical results obtained in this patient population. The specific objectives include: (i) a description of trends in the use of Impella devices, (ii) clinical characteristics of patients treated with the device, including an in-depth analysis of indications for treatment, (iii) evaluation of Impella treatment efficacy and safety, according to the prespecified endpoint definitions, along with identification of independent predictors of outcomes based on clinical and periprocedural data. The registry scheme is shown in Figure 1.

Selection of participants

The study population consists of consecutive patients treated with Impella in the course of high-risk PCI or cardiogenic shock.

The subgroup of patients undergoing Impella--assisted revascularization includes hemodynamically stable patients with severe CAD undergoing elective or urgent, high-risk PCI, when a heart team, including a cardiac surgeon, has determined high-risk PCI is the appropriate therapeutic option. The Impella therapy will be used for temporary MCS to prevent hemodynamic instability, which can result from repeat episodes of reversible myocardial ischemia that occur during planned temporary coronary occlusions and may reduce peri- and post-procedural adverse events.

The subgroup of patients treated with Impella due to cardiogenic shock includes patients with ongoing cardiogenic shock that occurs immediately following acute MI or open-heart surgery or in the setting of cardiomyopathy, including peripartum cardiomyopathy, or myocarditis that is not responsive to optimal medical management and conventional treatment measures (including volume loading and use of pressors and inotropes, with or without IABP). Impella therapy will be used to improve organ perfusion and reduce ventricular loading necessary for heart recovery.

Study schedule

The data of consecutive patients treated with Impella between 2012 (introduction of the Impella device to Poland) until July 2021 are collected retrospectively. The follow-up data are collected until July 2022 to ascertain the 12-month follow-up of all patients, including the last patient included.

The registry has been launched under the patronage of the Association of Cardiovascular Interventions of the Polish Cardiac Society. The conducting of the study is coordinated by the 1st Chair and Department of Medical University of Warsaw. The capability of the coordinating center to initiate and execute the proposed project have been demonstrated with numerous previous registries launched by the coordinating center [25–27].

Data are collected in all Polish interventional cardiological centers which performed at least 5 interventions using Impella, i.e., 20 centers. The list of participating centers is available on the dedicated website of the registry (https://www.rejestrimpella.pl/). Site investigators enter the required data into password-protected, web-based electronic case report forms (eCRF). The eCRF is designed and maintained by a dedicated IT specialist. The quality of the collected data is monitored by an independent Study Monitoring Committee.

The following data are collected from the included patients: (i) demographical data, (ii) medical history and comorbidities, (iii) indications for Impella, (iv), baseline laboratory parameters, (v) scores (NYHA, EURO score II, SYNTAX score, Mehran risk score), (vi) echocardiography findings at admission, (vii) procedural details including type of Impella device, duration of support, access site, closure device, (viii) need for supportive treatment including extracorporeal membrane oxygenation (ECMO), IABP, invasive ventilation, catecholamine support, dialysis, (ix) medical therapy at baseline and during hospitalization, (x) efficacy of MCS using Impella determined as hemodynamic improvement and survival to hospital discharge, (xi) complications of MCS including acute renal dysfunction, aortic valve injury, bleeding, cardiogenic shock, cerebral vascular accident/stroke, death, hemolysis, limb ischemia, MI, renal failure, thrombocytopenia and vascular injury, (xii) clinical, laboratory and echocardiographic status at discharge. The 12-month follow-up data are collected from in-hospital and ambulatory medical records.

End-points

The study end-points are: (i) the trends in the use of Impella devices, (ii) clinical characteristics of patients treated with Impella, including treatment indications, and (iii) Impella treatment efficacy and safety. The clinical end-points will be prespecified and evaluated by an Independent Adjudication Committee.

Efficacy will be evaluated on the rate of in-hospital mortality, 1-year mortality and the composite of death, rehospitalization for heart failure, acute MI, stroke, left ventricular assist device (LVAD) implantation or heart transplant at 12-months. In addition, the need for cardiosurgical intervention, exacerbation of heart failure, acute MI, inflammatory complications, acute kidney injury and need for renal replacement therapy, need for mechanical ventilation, need for support escalation due to hemodynamic deterioration (use of advanced short-term mechanical support such as ECMO or long-term mechanical support such as surgical implantation of LVAD) will be assessed.

Safety will be evaluated based on the rate of device-related complications (bleeding or limb ischemia, complications requiring endovascular interventions, stroke, life-threatening bleeding, haemolysis, aortic injury).

Regarding the previously reported impact of the learning curve and low volume on the overall

outcomes, additional pre-specified sub-analyses will be performed: (i) comparison of the outcomes of patients undergoing Impella-assisted interventions per year, from 2012 to 2021, and (ii) comparison of the outcomes of patients undergoing Impella-assisted interventions in low-volume centers (< 10 interventions per year), medium volume centers (10–20 interventions per year) and high-volume centers (> 20 interventions per year).

All analyses will be done separately for the use of Impella in patients undergoing high-risk PCI procedures and those with cardiogenic shock or other indications, as these are different conditions with different outcome expectations.

Statistical analysis

Statistical analysis will be conducted using IBM SPSS Statistics, version 24.0. Categorical variables will be summarized using frequencies and proportions and compared using the χ^2 test or the Fisher exact test, as appropriate. Continuous data will be summarized using mean ± standard deviation or median and interquartile range and compared using Student t-test or nonparametric U-Mann-Whitney test, depending on the type of distribution. The Kaplan-Meier method will be used to estimate overall and event-free survival and the log-rank test to compare survival distributions. The Cox proportional hazards model will be used to estimate predictors of mortality. All analyzes will be performed in a blinded manner regarding patient demographics by an independent statistician. Statistical tests will be two-sided, with a significance level of 0.05.

Legal considerations

The study protocol was approved by the Bioethical Committee of the Medical University of Warsaw. The study is conducted according to Good Clinical Practice, the ethical principles described in the Declaration of Helsinki, the requirements of the European Medicines Agency and local legal and regulatory requirements. Data storage is conducted in compliance with local data protection laws. Authorities may request access to the study documentation in case of an inspection or audit. Documentation can be copied during inspection or audit only in cases where the identity of the participant/s have been made unrecognizable.

Discussion

The IMPELLA PL registry is a unique registry specifically providing insights into a rapidly evolving Impella hemodynamic technology, increasingly used in a variety of applications. Hitherto, only three registries which focus specifically on Impella devices have been launched, collecting data from the population of Italian, German and US patients [21–23]. However, regarding the differences in clinical practice in Europe and the US and the fact that large randomized trials of hemodynamic support in patients undergoing high-risk PCI and with cardiogenic shock are challenging to conduct, it is crucial to establish new national and international registries to provide high quality data which would provide a solid base to support decision making and evidence-based recommendations. The preliminary experience of the present study group and the collaborating groups regarding the use of Impella have been published, mostly as case reports and case series', demonstrating the great interest of numerous investigators in Poland to perform Impella®-assisted interventions and accounting for the feasibility to perform this project [24, 28–31].

The proposed study has several limitations that need to be disclosed. Given its observational, non-randomized design, the findings will remain hypothesis-generating. However, they may be used to inform further studies in this field. Data collection will be retrospective and therefore subject to recall and ascertainment bias. In addition, in view of its retrospective design, despite the prespecified definitions of endpoints, event monitoring will not be standardized across clinical centres which may lead to underreporting of adverse events. Still, summary of the data from all patients treated with Impella over the last years in Poland will enable us to expand from the preliminary data derived from case reports to a national cohort analysis. In the future, data from the IMPELLA-PL registry could be linked to other national and international registries to expand the knowledge on Impella hemodynamic technology by sharing the obtained scientific and clinical experiences with other centers. Based on the retrospective results, the plan is to continue the registry in a prospective form, specifically targeting issues and problems identified in the retrospective phase of the study.

Altogether, the IMPELLA-PL registry will provide an extended evaluation of the Impella technology in various clinical scenarios, allowing for the optimization of treatment in patients with cardiogenic shock or undergoing high-risk PCI.

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Conflict of interest: None declared

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TECHNOLOGY NOTE

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Three-dimensional transesophageal echocardiography guided endomyocardial biopsy in diagnosis of cardiac tumor

Krzysztof Ozierański[1], Ewa Szczerba[1], Agata Tymińska[1], Michał Marchel[1], Radosław Piątkowski[1], Romuald Wojnicz[2], Miłosz Jaguszewski[3], Marcin Grabowski[1]

[1]First Department of Cardiology, Medical University of Warsaw, Poland
[2]Department of Histology and Cell Pathology in Zabrze, School of Medicine with the Division of Dentistry, Medical University of Silesia in Katowice, Poland
[3]First Department of Cardiology, Medical University of Gdansk, Poland

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Primary malignant cardiac tumors are extremely uncommon (< 0.3% of cardiac tumors in postmortem studies) and are associated with poor prognosis [1, 2]. Therefore, to increase the survival rate, an early and effective diagnostic process is necessary. Although noninvasive imaging modalities are useful, a definite diagnosis in most cases requires histologic examination, which remains a gold standard. Reported herein, is a patient with new-onset heart failure (HF), in which three-dimensional (3D) transesophageal echocardiography (TEE)-guided endomyocardial biopsy (EMB) confirmed the diagnosis of cardiac angiosarcoma.

The 73-year-old female with no relevant past medical history was admitted to the hospital due to signs of HF de novo. On admission, she presented shortness of breath upon exertion (New York Heart Association class II); heart rate, 90 beats/min; blood pressure, 95/78 mmHg; systolic-diastolic murmur on cardiac auscultation; general peripheral edema; signs of bilateral pleural effusion and liver enlargement. Laboratory studies showed elevated cancer biomarker: Ca-125, 290 U/mL (N: < 35 U/mL).

Transthoracic echocardiography (TTE) and TEE revealed a large mass with heterogeneous echogenicity almost completely filling the cavity of the right atrium (RA), infiltrating its wall, the visceral pericardium of the right ventricle and the apex of the heart causing severe obstruction of the inflow from both venae cavae with a mean gradient difference of 7 mmHg (Fig. 1).

Chest, abdomen, and pelvis contrast-enhanced computed tomography confirmed a large polycyclic tumor (88 × 67 × 74 mm) with heterogeneous densities in the RA and its surroundings. Cardiac magnetic resonance (CMR) was not performed on this patient because of kidney insufficiency.

As the primary differential diagnosis suggested a primary or secondary malignant cardiac tumor, a TEE-guided EMB from the access point of the right internal jugular vein was performed. Biopsy forceps (Cordis Corp) were inserted into a 7F (Cordis Corp) long sheath and advanced into the RA. The TEE allowed detailed visualization of the tumor, bioptome position on the tumor surface, and exact selection of the sample site. Periprocedural imaging was further enhanced with the use of 3D imaging (Fig. 1). Ten tissue samples were gathered from the tumor surface without periprocedural complications. Histochemistry, immunohistochemistry, and electron microscopy study of the EMB specimens revealed malignant vascular tumor features (Fig. 2).

The diagnostic and therapeutic approach of cardiac tumors is very demanding because of the various clinical presentation and intracardiac localization [3]. An early diagnosis of angiosarcoma is crucial for managing therapeutic options and the patient's prognosis.

Address for correspondence: Ewa Szczerba, MD, PhD, First Department of Cardiology, Medical University of Warsaw, ul. Banacha 1a, 02–097 Warszawa, Poland, tel: +48 22 599 29 58, e-mail: ewa_szczerba@poczta.onet.pl

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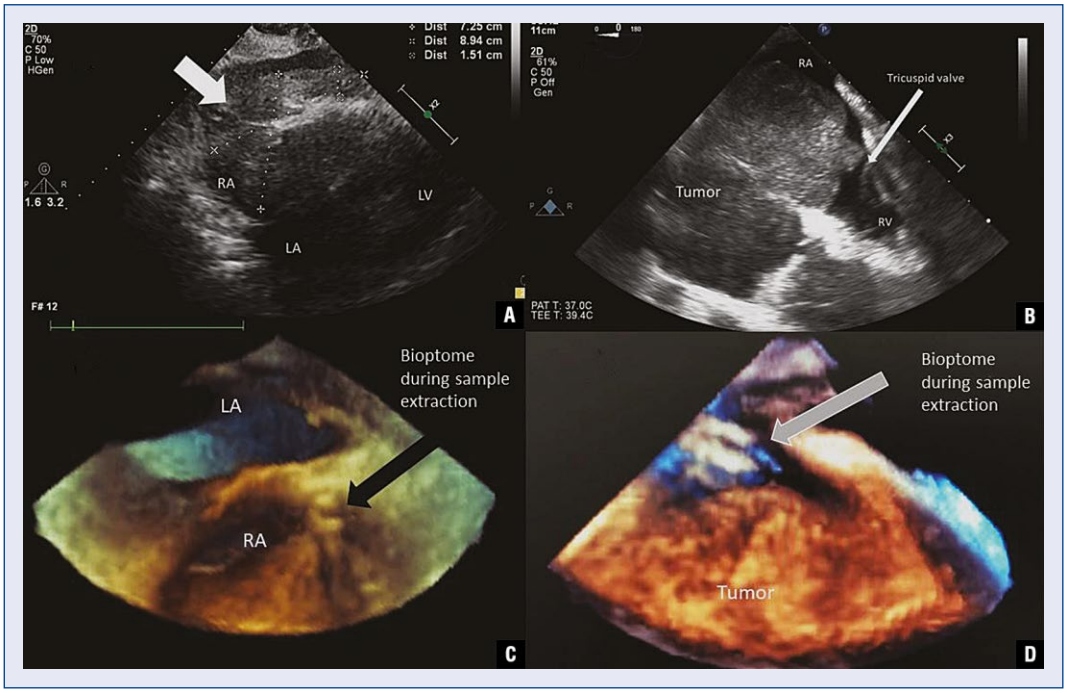

Figure 1. Imaging of the tumor; **A.** Large tumor with heterogeneous echogenicity (shown with a white arrow) infiltrating the wall of the right atrium (RA) and filling its cavity almost completely, visible from the substernal view in transthoracic echocardiography; **B.** Visualization of relation between tumor and tricuspid valve in transesophageal echocardiography (TEE); **C, D.** Three-dimensional TEE imaging showing exact localization of bioptome during extraction of tumor tissue samples; LA — left atrium; LV — left ventricle; RV — right ventricle.

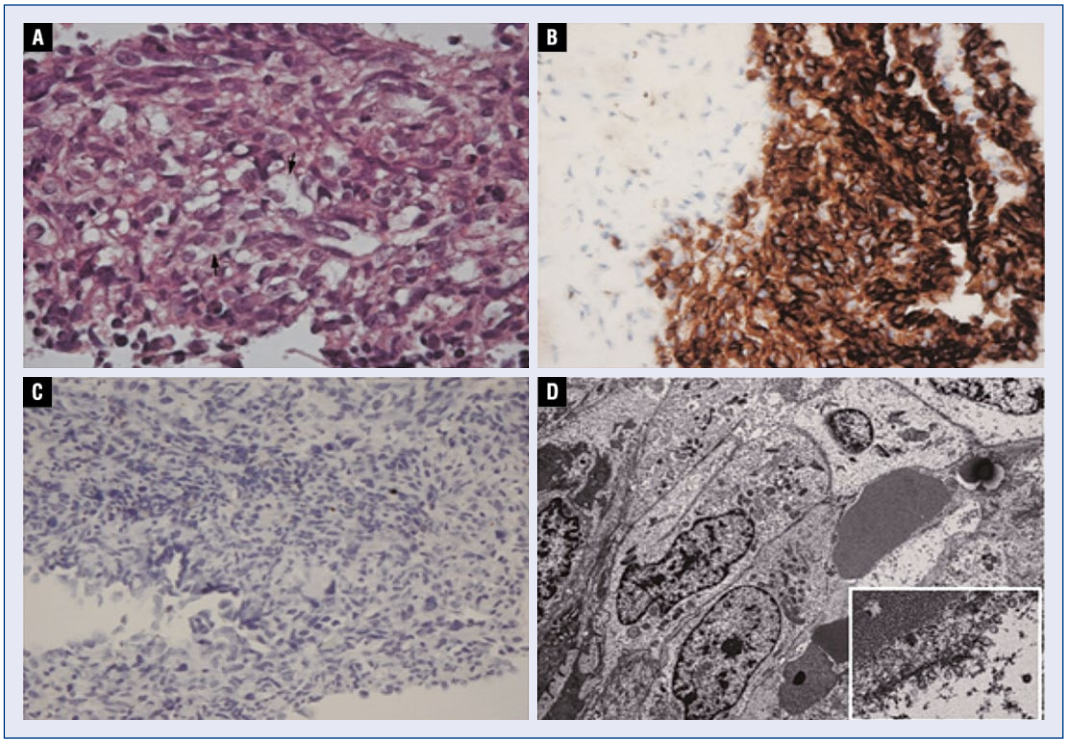

Figure 2. Primary cardiac angiosarcoma; **A.** Anaplastic cells with poorly formed vascular channels (arrows) (hematoxylin and eosin); **B.** Strong immunohistochemical staining for CD31 marker (brown color); **C.** Negative immunohistochemical staining for cytokeratin filaments AE1/AE3 (brown color); **D.** Electron micrographs showing immature endothelial cells.

Comprehensive clinical and multimodality imaging evaluation of cardiac tumors, including echocardiography, contrast enhanced computed tomography and CMR, is fundamental to obtain a proper initial differential diagnosis [4]. Angiosarcomas are mostly immobile and broad-based with endocardial to myocardial growth, however not all tumors infiltrate surrounding tissue [1]. CMR findings in angiosarcomas include heterogeneous T1- and T2-weighted signal intensity and a heterogeneous contrast enhancement pattern [1]. A position emission tomography scan with the use of 18F-2-fluoro-2-deoxy-D-glucose (FDG) can reveal areas of high FDG uptake within the mass and evidence of metastatic disease [5, 6].

Histopathological confirmation is needed for chemotherapy initiation and assessment of prognosis. In some cases, samples are obtained during cardiac surgery that is performed to remove the tumor but in patients disqualified from surgical treatment EMB is the only way to obtain tissue samples and a definite diagnosis. Despite a very low complication rate (< 1%), it is not commonly performed [7, 8]. EMB using broad histologic and immunohistochemical methods allows for the definition of the type of tumor, management of the treatment methods, and better risk stratification. Echocardiography-, electroanatomic mapping- or in the future, CMR-guided EMB increases the accuracy and safety of the procedure [9]. In the present case, TEE guidance allowed direct visualization of the tumor and bioptome position on its surface. The procedure proved that biopsy forceps, when guided by TEE, are feasible for the diagnosis of intracardiac tumors. The use of 3D TEE indicated the place of sample collection and minimized the risk of complications. 3D visualization ensures permanent visualization of the biopsied tissue in a pumping heart. This was crucial since the RA cavity was to a great extent occupied with the tumor and the targeted mass was in close proximity to the atrial septum and tricuspid valve leaflets. To increase the diagnostic accuracy and sampling error, it is necessary to gather at least five tissue samples (recommended 5–10), each 1–2 mm in size. The main limitation of EMB is a need for experienced physicians and histopathologists; thus, patients should be referred to tertiary medical centers.

In terms of treatment, angiosarcomas, when localized without infiltration of adjacent structures, may undergo surgery with or without upfront chemoradiotherapy. The majority of angiosarcomas have a poor overall prognosis related to EMB--targeted therapeutic management and complete surgical resection of the tumor.

To conclude, this case report showed that EMB guided by TEE might increase the accuracy and safety of the procedure and enable a definite diagnosis of the type of intracardiac tumor, facilitating further management.

Ethical statement

The authors are accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest: None declared

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RESEARCH LETTER

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Heart valve disease in Hurler-Scheie syndrome

María del Carmen García del Rey[1, 3], Javier Castrodeza[1, 3], Ángel Pinto[2, 3], María Ángeles Espinosa Castro[1, 3], Cecilia Muñoz Delgado[4], Francisco Fernández-Avilés[1, 3]

[1]Cardiology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[2]Cardiac Surgery Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain
[3]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain
[4]Internal Medicine Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain

Mucopolysaccharidosis (MPS) syndromes are classified by six subtypes [1]. Mucopolysaccharidosis type I (MPS I) is an autosomal recessive hereditary disease, characterized by the accumulation of glycosaminoglycans (GAGs) in any tissue as a consequence of a decrease in the enzymatic activity of alpha-L-iduronidase [2]. Traditionally, MPS I has been classified into three subtypes based on the severity of the disease and the age of onset: Hurler syndrome, Hurler-Scheie syndrome and Scheie syndrome; but a recent classification has been shortened to two subgroups: severe MPS I or Hurler syndrome, and attenuated MPS I or Hurler--Scheie syndrome [3]. The former has an earlier onset of symptoms, while in the attenuated form the clinical presentation occurs in patients between 3 and 10 years of age and the neurological structures are intact. The life expectancy is short, especially in the severe form with a mean survival between 6 and 7 years, while in the attenuated form, patients can reach adulthood if they are treated with enzyme replacement therapy [4].

Cardiac involvement is common in MPS I [4, 5]. It is produced by the progressive infiltration of GAGs not only in the valves, but also in the myocardium, coronary arteries, and conduction system [4]. Approximately, half of patients with severe MPS I die from cardiac causes, congestive heart failure, or sudden death [4]. The most affected structure is the mitral valve followed by the aortic valve. It mainly affects the mitral chords resulting in decreased leaflet mobility [5, 6]. In this regard, a transoesophageal echocardiogram usually shows a myxomatous mitral valve with leaflet restriction, resulting in a double mitral valve lesion, both mitral stenosis and insufficiency as seen in Figure 1A, B (**Suppl. Video 1 and 2**). Consequently, surgical repair is not commonly feasible and mitral valve replacement is the usual and most durable approach [5]. Usually, the left atrium is not dilated, as well as the sinus aorta, which make the surgical approach more challenging for the cardiac surgeon [7]. Furthermore, calcium deposits on the mitral annulus are common, and this fact can interfere with prosthesis' sutures, requiring an annular reinforcement with a pericardial patch sometimes [7, 8]. Also, very shortened and thickened chords can be seen during surgery, accompanied by hypertrophic papillary muscles as seen in Figure 1C (**Suppl. Video 3**). All these features make it a very challenging scenario to propose mitral valve repair, leading to valve replacement in most cases.

As these patients have a small body size, small valves are required (generally the mean mitral size of the prostheses is 24 ± 2.2 mm, and aortic ones are 19 ± 0.5 mm) [8]. Arrhythmias and conduction disorders are also common, especially in MPS II, III and VI [5].

Regarding respiratory involvement, patients can present with a restrictive respiratory pattern. The trachea and bronchi are often thickened and infiltrated by GAGs and tracheomalacia can be present [4]. A chest computed tomography is advisable to rule out tracheomalacia (Fig. 1D, E) in order to ensure the absence of difficult airway management.

Address for correspondence: Javier Castrodeza, MD, PhD, Cardiology Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain, tel: (+34) 915868290, e-mail: jcastrodeza5@gmail.com

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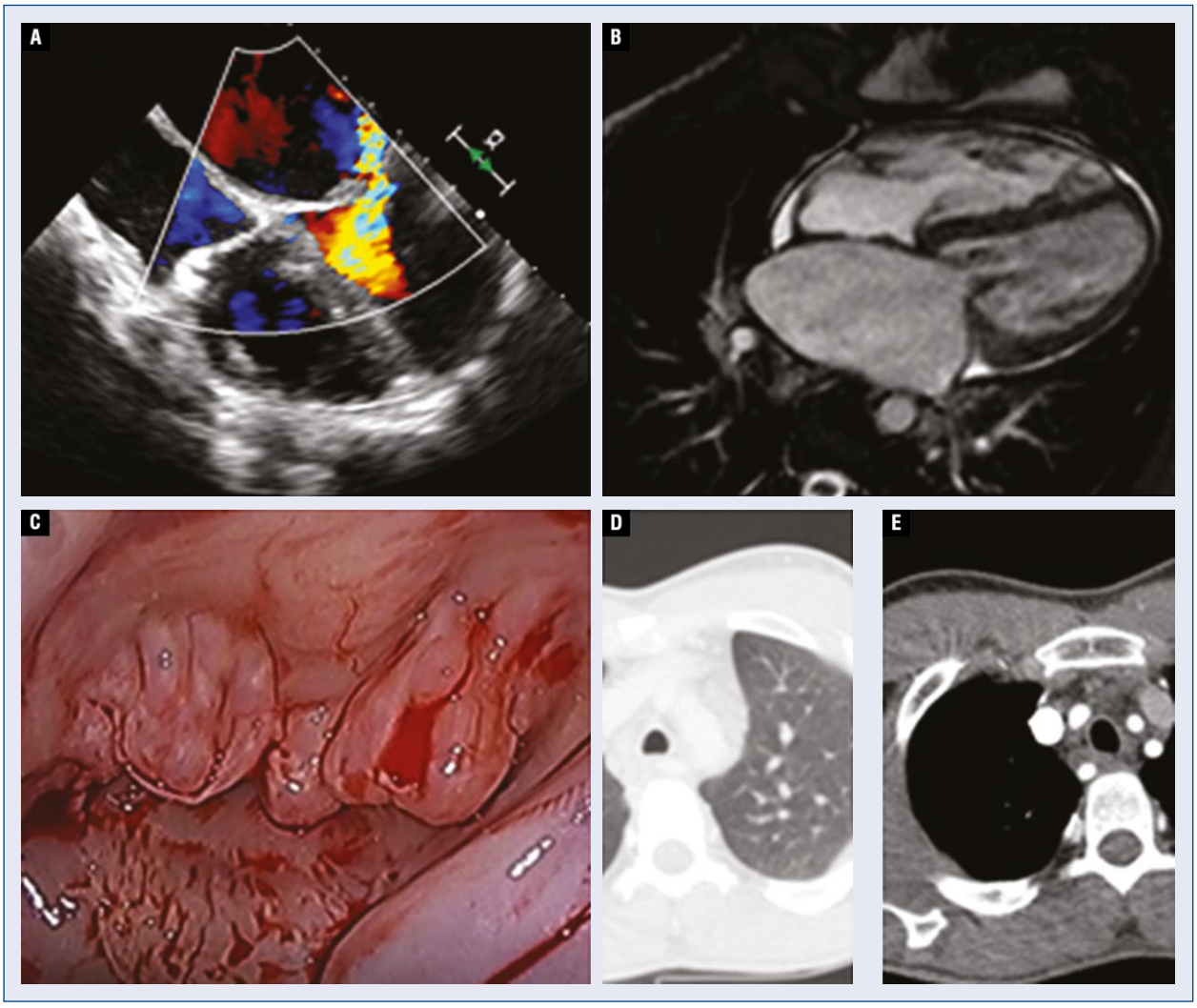

Figure 1. A. Four-chamber transoesophageal 0° view showing severe mitral regurgitation; **B.** Four-chamber magnetic resonance imaging view showing a dilated left atrium, a normal sized and not hypertrophic left ventricle, normal right chambers and a lateral jet of severe mitral regurgitation; **C.** Surgical view of a myxomatous mitral valve with shortened and thickened chords accompanied by hypertrophic papillary muscles; **D, E.** Chest computed tomography with no evidence of tracheomalacia in a patient with Hurler-Scheie syndrome.

A specific phenotype is usually present consisting in multiple dysostosis, upper and lower limb joint arthrogryposis, a sunken nasal bridge, corneal dystrophy, craniofacial abnormalities, short neck, prominent adenoids and tonsils, prominent macroglossia, glottis, and epiglottis [4]. As a result, patients usually develop obstructive sleep apnoea-hypopnea syndrome, recurrent upper airway infections, and recurrent rhinorrhea [4].

For all these reasons and due to the risk of spinal cord compression and atlas and axis vertebrae instability, anaesthetic induction and intubation are high-risk procedures [9].

The particular phenotypic feature can be a guide to establish a diagnostic suspicion. Some laboratory diagnostic methods such as the detection of heparan sulphate in urine testing can suggest the diagnosis and confirmation comes with a genetic test. There are known mutations associated with MPS, some of them are responsible for severe forms as pVal620Phe and p.Trp626Arg, while pArg619Gly and Ser633Leu are seen in attenuated forms. Nevertheless, if a histopathological analysis of the valve tissue is performed in cases of valve replacement, a marked GAG accumulation in the macrophage cytoplasm and valve stroma can be detected [10].

The course of the disease is chronic and progressive. There are two treatment options: bone marrow transplantation and enzyme replacement therapy.

Bone marrow transplantation is more effective at a younger age, however valvular involvement is usually resistant to it and often persists [4, 6]. Although the success of this therapy has increased during the recent years, the mortality rate is still quite high [9].

Enzyme replacement therapy with RL Aldurazyme® (laronidase) was approved in 2003 for exclusive use in MPS I and has emerged as a promising therapy [3]. Early treatment helps to stabilize lung disease, and slows down the tissue infiltration [3]. With regard to the heart involvement, it may decrease ventricular hypertrophy, but valve infiltration usually progresses despite treatment [3]. There is no identified interaction between the replacement therapy and vitamin K antagonist. Therefore, the combination of them can be done in patients with mechanical valve prostheses.

As a conclusion, valvular replacement in patients with MPS I remains a challenging scenario due to anatomical features and the multiorgan involvement of the disease, requiring a multidisciplinary coordination to achieve an optimal postoperative outcome. Enzyme replacement therapy slows down the tissue infiltration with a marginal effect on the valves. The mitral and the aortic valve are the most affected, requiring a valve replacement after the severity is established, oftentimes by a mechanical prosthesis due to the patients' young age.

Conflict of interest: None declared

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IMAGE IN CARDIOVASCULAR MEDICINE

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Acute myocardial injury as a sole presentation of COVID-19 in patient without cardiovascular risk factors

Dominika Filipiak-Strzecka[1], Michał Plewka[1, 2], Ewa Szymczyk[1], Karolina Frynas-Jończyk[1], Konrad Szymczyk[1], Piotr Lipiec[1], Jarosław D. Kasprzak[1]

[1]Department and Chair of Cardiology, Medical University of Lodz, Bieganski Hospital, Lodz, Poland
[2]Department of Interventional Cardiology and Cardiac Arrhythmias, Medical University of Lodz, Poland

A previously healthy 49-year-old male without cardiovascular risk factors was admitted to the cardiology ward with severe resting chest pain. No fever, cough or dyspnea was reported. electrocardiography examination showed ST segment elevation in the inferior leads. His troponin-T level was increasing from 16 to 266 ng/L. Markers and NT-pro-B-type natriuretic peptide levels were elevated. Urgent coronarography exposed no hemodynamically significant abnormalities (Fig. 1A, C). Persisting chest pain led to the angio-computed tomography (CT) and high resolution CT excluding pneumonia or acute aortic dissection. However, the patient tested positive for coronavirus disease 2019 (COVID-19) RT-PCR and was transferred to the COVID-19 cardiac ward. Echocardiography showed left ventricular (LV)-wall motion abnormalities within the inferolateral wall and septum, LV ejection fraction: 43% and LV global longitudinal strain: –14%. Five-day treatment with remdesivir was implemented. The initial diagnosis of myocarditis was proposed but magnetic resonance imaging (MRI) performed after 14 days showed subendocardial late gadolinium enhancement (50–75% wall thickness, locally transmural; Fig. 1E) in the middle and apical segments of inferolateral wall. Subendocardial high T2 signal intensity indicated myocardial edema (Fig. 1F, G). As MRI was strongly suggestive for ischemic lesion, coronarography was reassessed and an overlooked minor posterolateral branch thrombus with late phase contrast retention was detected. Thus, final diagnosis was COVID-19-related thrombotic coronary occlusion (Fig. 1B). After 15 days the patient was discharged in a good general condition. One-year follow-up echocardiography confirmed persisting small (< 1 segment) hypokinetic area with abnormal local strain and recovered global LV function (Fig. 1D). This report highlights difficult differential diagnosis of acute cardiac injury in COVID-19, in this case due to an unexpected intracoronary thrombosis in normal coronary arteries.

Conflict of interest: None declared

Address for correspondence: Dominika Filipiak-Strzecka, PhD, Chair and Department of Cardiology, Medical University of Lodz, Bieganski Hospital, ul. Kniaziewicza 1/5, 91–347 Łódź, Poland, tel/fax: +48 42 2516216, e-mail: dominika.filipiak@gmail.com

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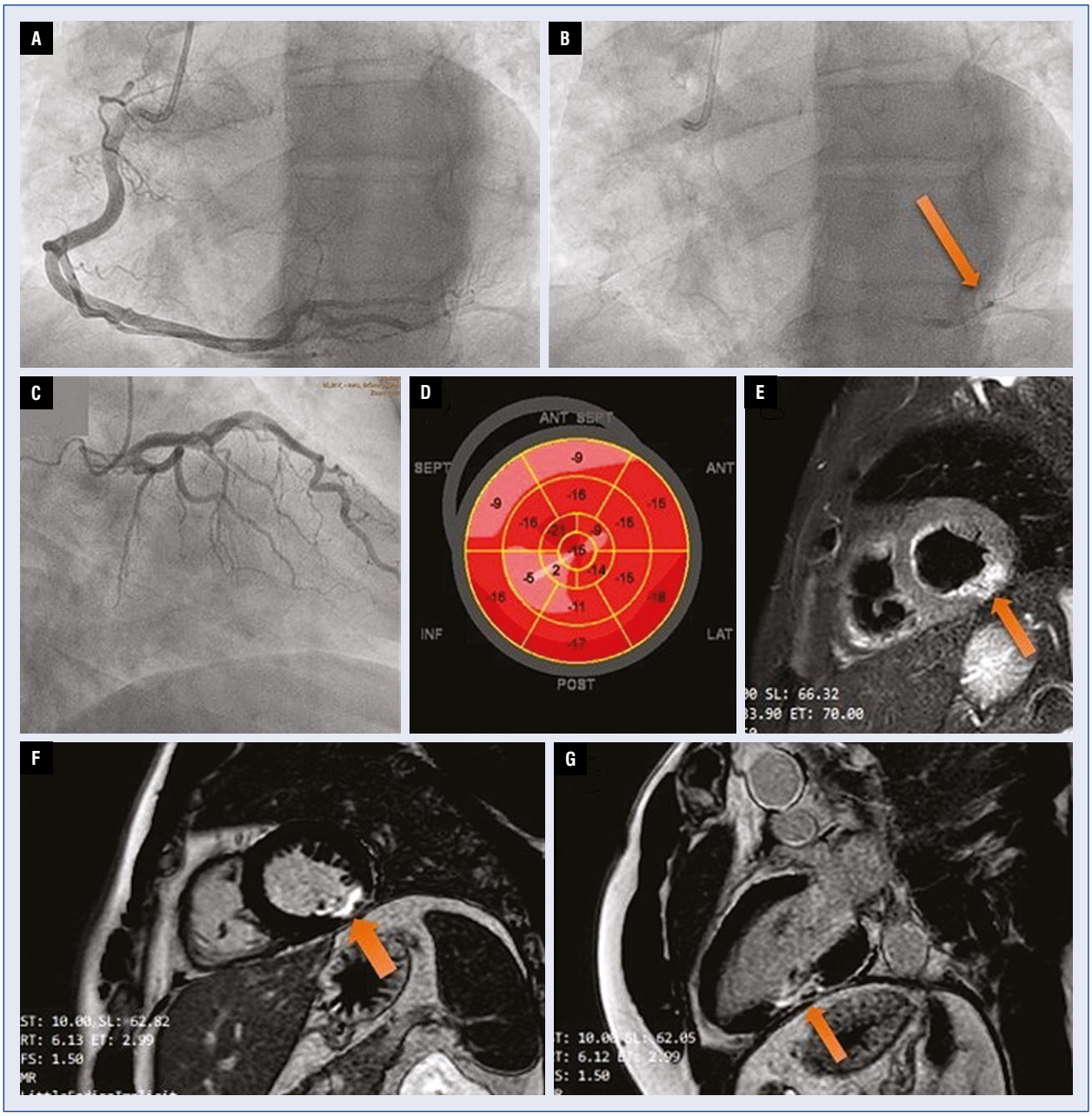

Figure 1. A–C. Views from coronarography; **A.** Right coronary artery, early phase of contrast enhancement; **B.** Right coronary artery, late phase, contrast retention in a minor posterolateral branch marked with an arrow; **C.** Normal left coronary artery with recessive circumflex artery; **D.** Echocardiographic examination after one year, bullseye view showing small region of abnormal local strain located in the inferolateral wall; **E–G.** Cardiac magnetic resonance views; **E.** Subendocardial late gadolinium enhancement detected in the middle and apical segments of inferolateral wall (marked with an arrow); **F, G.** Subendocardial high T2 signal intensity indicated myocardial edema (arrows).

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IMAGE IN CARDIOVASCULAR MEDICINE

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Tricuspid valve resection without replacement: An asymptomatic severe right ventricle dysfunction 16 years after surgery

Aleksander Olejnik[1], Andrzej Kułach[2], Michał Kucio[1], Mariusz Bałys[1], Maciej Haberka[2], Zbigniew Gąsior[2]

[1]2nd Department of Cardiology, Upper Silesian Medical Center, Katowice, Poland
[2]Department of Cardiology, SHS, Medical University of Silesia in Katowice, Katowice, Poland

Presented herein, is the case of a 33-year-old patient with a history of tricuspid valve (TV) endocarditis and subsequent complete resection of the anterior and posterior leaflet at the age of 17, without the TV replacement. Due to an asymptomatic post-op course, he had been lost to follow-up for 16 years. Subsequently, he was referred with mild heart failure symptoms (NYHA I, no peripheral edema). His NT-pro-B-type natriuretic peptide was mildly elevated (555 pg/mL) and did 625 m on a 6-minute-walk-test.

Echocardiography showed enlarged right ventricle (RV) (RVIT: 96 mm, RVOT: 58 mm), severe tricuspid regurgitation (TR), and D-shaped left ventricle with left ventricular ejection fraction 45%. A cardiac magnetic resonance (CMR) confirmed massively enlarged RV (RVEDV: 847 mL, RVESV: 516 mL, RVEF: ~40%) and severe TR (TRvol: > 200 mL) with complete destruction of the leaflets. Right heart catheterization revealed elevated mean pulmonary artery pressure (30 mmHg), increased pulmonary capillary wedge pressure (20 mmHg), with preserved cardiac output (4.8 L/min). Due to severe RV dysfunction patient was not qualified for cardiac surgery and was referred to a heart transplant center. He remains asymptomatic on pharmacological management (Fig. 1A–D).

Although a complete TV resection without replacement is feasible, it leads to progressive right-sided heart failure and should not be a target strategy. In this case, severely enlarged right chambers, RV overload and ventricular interdependence led to moderate left ventricular dysfunction and pulmonary hypertension. Young age and lack of concomitant diseases explain the asymptomatic presentation, which is hard to believe looking at the images in CMR. This is, however, likely to worsen over time, leaving open the question of further management, including the right timing for a heart transplant.

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Address for correspondence: Andrzej Kułach, MD, PhD, Department of Cardiology, School of Health Sciences, Medical University of Silesia in Katowice, ul. Ziołowa 47, 40–635 Katowice, Poland, tel: +48 505863793, e-mail: andrzejkulach@gmail.com

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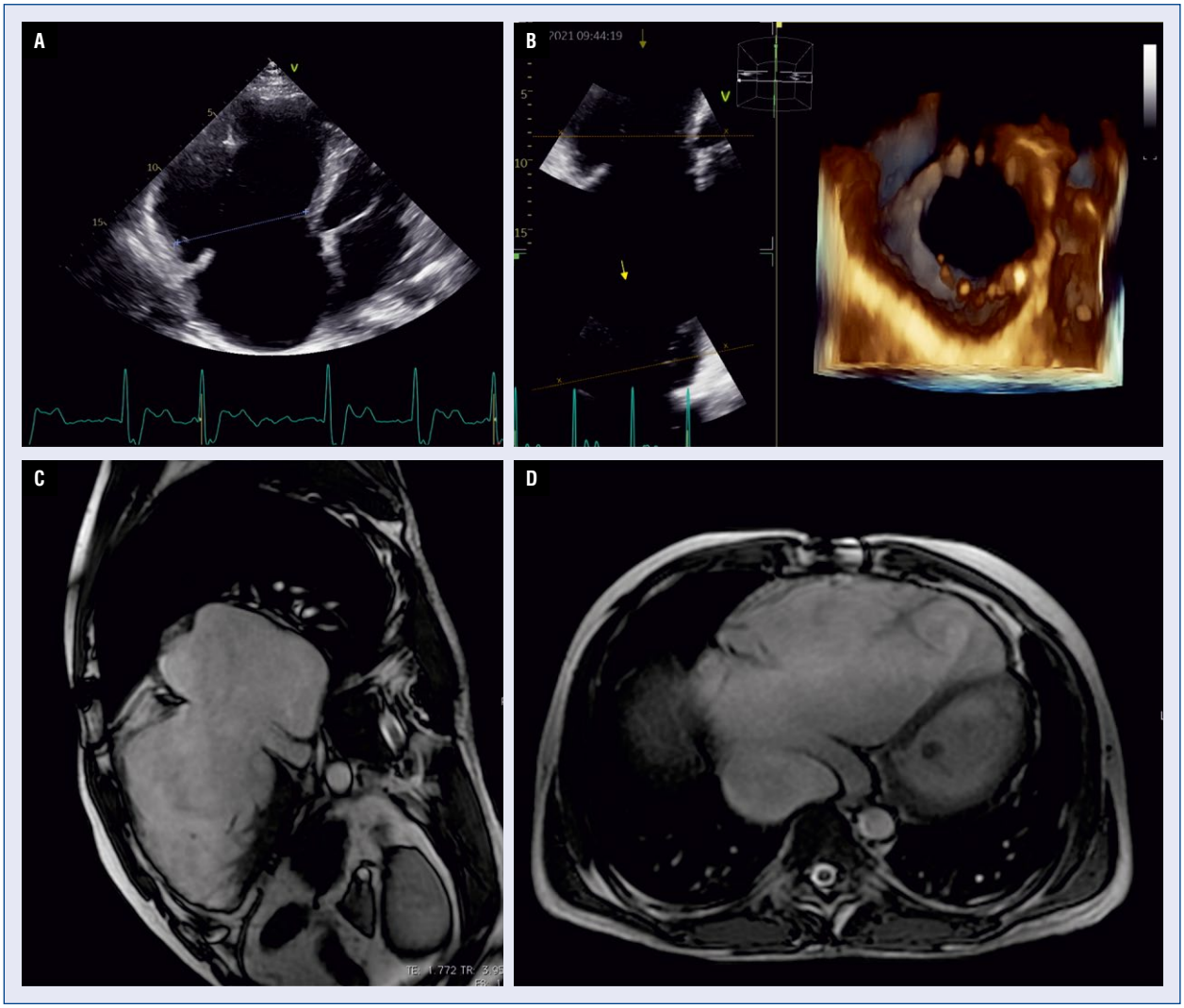

Figure 1. A. Transthoracic echocardiography. Apical four-chamber view. Enlarged right ventricle and right atrium. Right ventricle/left ventricle ratio > 1. Only small remains of the tricuspid valve leaflets are seen. Interatrial septum bows toward the left atrium; **B.** Three-dimensional echocardiographic imaging from a transthoracic approach. Fragments of the tricuspid valve seen from the right ventricle; **C, D.** Magnetic resonance imaging of the right heart (C: two-chamber view, D: four-chamber view).

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

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Flail tricuspid valve with torrential regurgitation caused by papillary fibroelastoma

Lingyun Fang[1, 2]*, Wenqian Wu[1, 2]*, Jing Wang[1, 2], Mingxing Xie[1, 2]

[1]Department of Ultrasound Medicine, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
[2]Hubei Province Key Laboratory of Molecular Imaging, Wuhan, China

A 51-year-old male patient was admitted to our hospital with chest tightness, palpitation, and edema of both lower extremities. Transthoracic echocardiography showed flail tricuspid valve (TV) with torrential regurgitation, right ventricular dilation, and dysfunction (Fig. 1A–D, **Suppl. Video S1**). Furthermore, an echodense structure at the tips of the flail leaflet was identified as ruptured papillary muscle or chordae tendineae, which was thought to be the cause of torrential regurgitation (Fig. 1A, B). Transesophageal echocardiography confirmed tricuspid dysfunction and increased echodensity at the edge of the TV (Fig. 1E, F). The patient underwent tricuspid surgery. Intraoperative exposition of the TV showed a small mass on the cuspid-chordal junction of the anterior leaflet and involved chordae tendineae (Fig. 1G). Valve repairment was tried and failed during the procedure. Finally, a tricuspid bioprosthesis was implanted. The patient tolerated the procedure well. A pathological assessment of the resected mass determined it to be an unexpected papillary fibroelastoma (Fig. 1H).

Cardiac papillary fibroelastoma (CPF) is a rare primary benign tumor typically located on leaflets of the valve. Most CPF is asymptomatic and is incidentally found by autopsy. Typical echocardiographic features include a small, mobile mass with a pedicle attached to the leaflets. In this case, the neoplasm mimicked ruptured papillary muscle or chordae tendineae and had failed to be diagnosed by echocardiography. The challenge is that the mass was tiny and not easily identified as a neoplasm. This highlights the possibility of CPF is rare and a cause which severely affects tricuspid function, even in the absence of a significant mass on echocardiography.

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Address for correspondence: Jing Wang, MD, PhD, 1277 Jiefang Avenue, Wuhan, 430022, China, tel: 86-27-85726430, fax: 86-27-85726386, e-mail: jingwang2004@hust.edu.cn; Mingxing Xie, MD, PhD, 1277 Jiefang Avenue, Wuhan, 430022, China, tel: 86-27-85726430, fax: 86-27-85726386, e-mail: xiemx@hust.edu.cn

**Co-first author: Lingyun Fang, MD, PhD; Wenqian Wu, MD, PhD*

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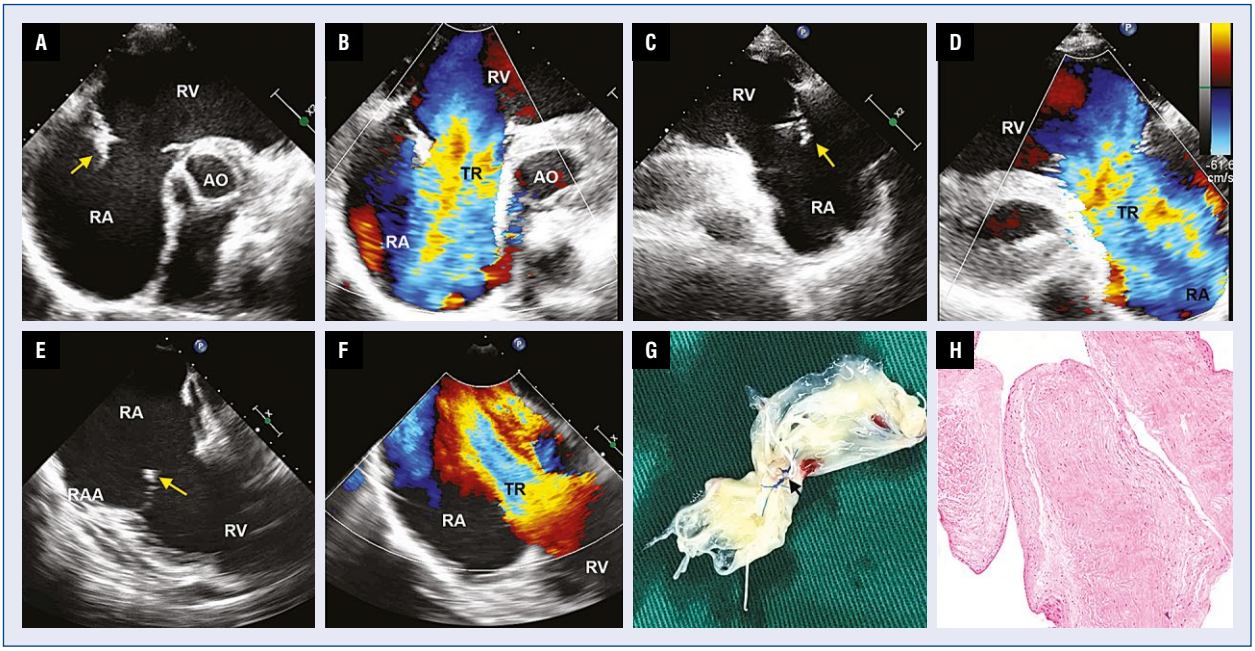

Figure 1. Echocardiographic, intraoperative, and histopathological images. Transthoracic and transesophageal echocardiography shows the flail tricuspid valve and an echodense structure at the tips of the flail leaflet (yellow arrows) (**A**, **C**, **E**). The corresponding color Doppler images reveal the torrential regurgitation (**B**, **D**, **F**). Intraoperative photograph of the removed tricuspid valve and a tiny mass involving chordae (black arrow) (**G**). Histopathological examination in hematoxylin and eosin stain at 200 magnifications shows multiple avascular connective tissues surrounded by a single layer of endothelial cells (**H**); AO — aorta; RV — right ventricle; RA — right atrium; RAA — right atrial appendage, TR — tricuspid regurgitation.

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Percutaneous left atrial appendage closure containing thrombus

Mohsen Mohandes[1], Cristina Moreno[1], Marta Guillén[2], Leydimar Anmad Shihadeh[2], Diego Zambrano[1]

[1]Interventional Cardiology Unit, Cardiology Division, Joan XXIII University Hospital, Pere Virgili Health Research Institute (IISPV), Tarragona, Spain
[2]Cardiology Division, Joan XXIII University Hospital, Pere Virgili Health Research Institute (IISPV), Tarragona, Spain

An 85-year-old man with permanent atrial fibrillation was referred to our institution for percutaneous left atrial appendage (LAA) closure (LAAC). The patient had chronic renal disease (CRD) with glomerular filtration rate (GFR) 25 mL/min and under acenocumarol therapy had developed melaena due to colonic angiodysplasia with severe anemia (hemoglobin: 5.9 g/dL). Transesophageal echocardiography (TEE) revealed thrombus within LAA (Fig. 1A). LAAC using simultaneous cerebral protection with Sentinel™ (Claret Medical, Santa Rosa, CA, USA) was scheduled. The procedure was performed under general anesthesia and guided by TEE. After transseptal puncture, heparin was administered and afterward Sentinel™ was inserted through right radial artery (Fig. 1B). A LAmbre™ (Lifetech Scientific Corp., Shenzhen, China) 24/30 mm for LAAC was chosen and contrast medium injection was avoided during the procedure. A partial umbrella delivery of LAmbre was carried out in front of the LAA and the whole system was advanced slowly within LAA trying not to touch the thrombus (Fig. 1C). Initially, the umbrella position seemed to be a little deep so the umbrella was partially recaptured and delivered again in a better position. Afterward, the cover part of the device was delivered and pulled back slightly so to achieve a proper positioning. TEE confirmed an adequate position and absence of any leakage while tug test manoeuver revealed the device's stability. Hence, the LAmbre was ultimately released without incidence (Fig. 1D, **Suppl. Video 1**). Sentinel™ was retrieved and no debris was identified in the system. The patient post-intervention course was uneventful.

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Address for correspondence: Mohsen Mohandes, MD, PhD, Interventional Cardiology Unit, Cardiology Division, Joan XXIII University Hospital, Pere Virgili Health Research Institute (IISPV), Tarragona, Spain, tel: 0034-977295817, e-mail: mohandesmohsen@hotmail.com

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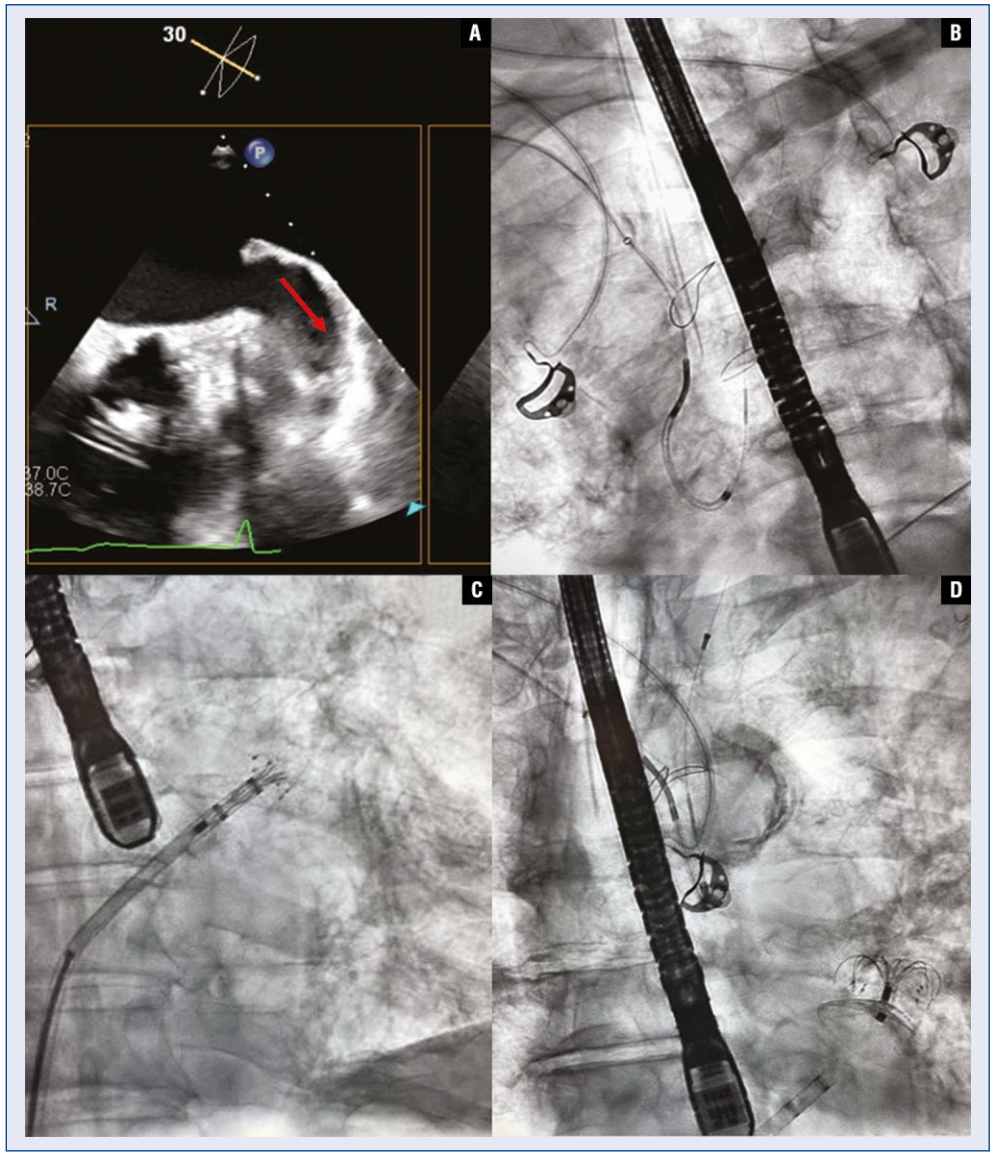

Figure 1. A. Left atrial appendage shows thrombus at its bottom; **B.** Sentinel with its two baskets is inserted into the right brachiocephalic trunk and left carotid artery; **C.** Partial delivery of umbrella in the left atrial appendage; **D.** Complete release of the device, showing umbrella and cover part in a good position.

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Cardiac arrest outcomes in the COVID-19 era

Sina Salajegheh Tazerji[1, 2], Alla Navolokina[3], Eryka Karbowska[4], Fatemeh Shahabinejad[5]

[1]Department of Clinical Science, Faculty of Veterinary Medicine, Science and Research Branch, Islamic Azad University, Tehran, Iran
[2]Young Researchers and Elites Club, Science and Research Branch, Islamic Azad University, Teheran, Iran
[3]Department of Public Health and Social Medicine, International European University, Kyiv, Ukraine
[4]Maria Sklodowska-Curie Bialystok Oncology Center, Bialystok, Poland
[5]Kerman Medical University, Kerman, Iran

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it causes coronavirus disease 2019 (COVID-19) has constituted a major challenge over the past 2 years and will continue to be challenging for healthcare professionals into the future [1, 2]. The SARS-CoV-2, as indicated by numerous scientific publications, causes havoc not only in the respiratory system, but also in the cardiovascular system. SARS-CoV-2 has an affinity for heart muscle cells; therefore, it also poses a risk of developing cardiological complications, including myocardial infarction, arrhythmias and heart failure. In addition, due to the damage to blood vessels and affects to blood clotting disorders, the risk of thromboembolic complications also increases [3]. Undoubtedly, however, the greatest risk is the risk of cardiac arrest.

It is true that the survival of patients in cardiac arrest are influenced by many factors, including factors related to the presence of comorbidities, the time from cardiac arrest to the initiation of resuscitation, and the quality of resuscitation. For both out-of-hospital cardiac arrest and in-hospital cardiac arrest, healthcare professionals should treat each patient as potentially infectious until COVID-19 has been ruled out and cardiopulmonary resuscitation (CRP) should therefore be performed wearing personal protective equipment for aerosol generating procedures [4]. In out-hospital cardiac arrest (OHCA) cases, due to the need to prepare medical personnel, including wearing personal protective equipment-aerosol generating procedure (PPE-AGP), the travel time to the patient is extended — so his chances of survival decrease with each minute of not taking CRP [5]. On the other hand, the mere performance of medical procedures, including chest compression, or securing the airways by medical personnel wearing PPE-AGP, may reduce the effectiveness of individual medical procedures [6].

SARS-CoV-2 itself, as shown by numerous studies, also adversely affects the prognosis of patients with cardiac arrest. In a meta-analysis by Bielski et al. [7] regarding OHCA survival before and during the COVID-19 pandemic, the authors showed that the survival to hospital discharge was 11.5% and 8.2%, respectively, before the pandemic and during the pandemic. Bielski et al. [7] also showed a significant impact of COVID-19 on the 30-day survival rate in this group of patients, where during the COVID-19 pandemic this survival rate was 2.8% lower than in the corresponding period before the pandemic. In turn, Borkowska et al. [8] analyzing the departure of the ambulance service in the first months of the COVID-19 pandemic to patients with OHCA, indicates a very low percentage of return of spontaneous circulation, amounting to only 9.4%. In turn, Szarpak et al. [9] in the

Address for correspondence: Dr. Sina Salajegheh Tazerji, Department of Clinical Science, Faculty of Veterinary Medicine, Science and Research Branch, Islamic Azad University, Tehran, Iran; Young Researchers and Elites Club, Science and Research Branch, Islamic Azad University, Teheran, Iran, tel: +98 9356923189, e-mail: sina.salajegheh@gmail.com; sina.salajegheh@srbiau.ac.ir

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meta-analysis on in-hospital cardiac arrest, patients indicate a slightly higher survival of patients in the period preceding the pandemic than during COVID-19 (35.6% vs. 32.1%, respectively; p = 0.16).

In conclusion, when using PPE-AGP, medical personnel during CPR should use devices that will increase the effectiveness of resuscitation. Thus, in terms of airway management — supraglottic ventilation devices or video laryngoscopes and mechanical chest compression systems should be used for chest compression [10].

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The answer to the riddle: Multimodality imaging for diagnosing a double hit of acute coronary syndrome and takotsubo syndrome

Peter Laurenz Dietrich[1], Maciej Cieslik[2], Victoria L. Cammann[2, 3], Stephan Schneiter[4], Matthias R. Meyer[4, 5], Christian Templin[2, 3]

[1]Triemli City Hospital Zurich, Division of Cardiology, Zurich, Switzerland
[2]University Hospital Zurich, University Heart Center – Department of Cardiology, Zurich, Switzerland
[3]University of Zurich, Zurich, Switzerland
[4]Cantonal Hospital of Grisons, Division of Cardiology, Chur, Switzerland
[5]Institute of Primary Care, University of Zurich and University Hospital Zurich, Zurich, Switzerland

Diagnosing the cause of a non-ST-segment elevation myocardial infarction (NSTEMI) may be challenging in the absence of clear angiographic signs of plaque rupture. Heitner et al. [1] demonstrated how delayed-enhancement cardiac magnetic resonance imaging (DE-CMR) identified a new culprit lesion or revealed a non-ischemic cause in nearly half of studied NSTEMI patients compared with judgment by coronary angiography alone. In the presented case of an older man with a NSTEMI, imaging modalities helped us to diagnose the underlying pathological mechanisms in the rare circumstance of a double hit by an acute coronary syndrome (ACS) and takotsubo syndrome (TTS).

A 75-year-old male patient initially presented at an external hospital with chest tightness and dyspnea for several hours. The patient was pain free at presentation and the clinical examination was unremarkable. Cardiac biomarkers were elevated [high-sensitive troponin T: 868 ng/L (normal < 14 ng/L); creatine kinase: 963 U/L (normal < 308 U/L)]. Electrocardiogram (ECG) initially showed non-significant ST-segment elevations in the inferior leads and slight T-wave alterations in leads V5–6. An ECG several hours later demonstrated dynamic changes with T-wave inversions in the majority of leads (except aVR, aVL and V1–2). The patient was referred to our hospital for coronary angiography that revealed severe three-vessel disease with normal coronary artery flow, but severe stenoses in all three major vessels (Fig. 1A–C). Left ventriculography showed a moderately reduced left ventricular ejection fraction (LVEF) with apical ballooning (Fig. 1D–F) consistent with TTS and extending beyond the vascular distribution of the left anterior descending artery (LAD). There were no clinical or angiographic signs of ongoing ischemia and due to the equivocal findings, the decision was made to perform a DE-CMR to differentiate between TTS and ACS. Meanwhile, therapeutic heparin and acetylsalicylic acid were continued, and an angiotensin-converting enzyme inhibitor was started.

Surprisingly, DE-CMR showed not only extensive myocardial edema of the midventricular and apical segments consistent with TTS (Fig. 1G), but also late gadolinium-enhancement of the mid-ventricular and apical inferolateral wall suggestive of myocardial infarction in the territory of the right coronary artery (RCA) or left circumflex artery (Fig. 1H).

Only few hours after CMR, the patient developed an acute infero-posterior ST-segment eleva-

Address for correspondence: Christian Templin, MD, PhD, FESC, Professor of Cardiology, Director Andreas Grüntzig Heart Catheterization Laboratories, University Hospital Zurich, University Heart Center – Department of Cardiology, Raemistrasse 100, 8091 Zurich, Switzerland, tel: +41 (0)44 255 9585, e-mail: Christian.Templin@usz.ch

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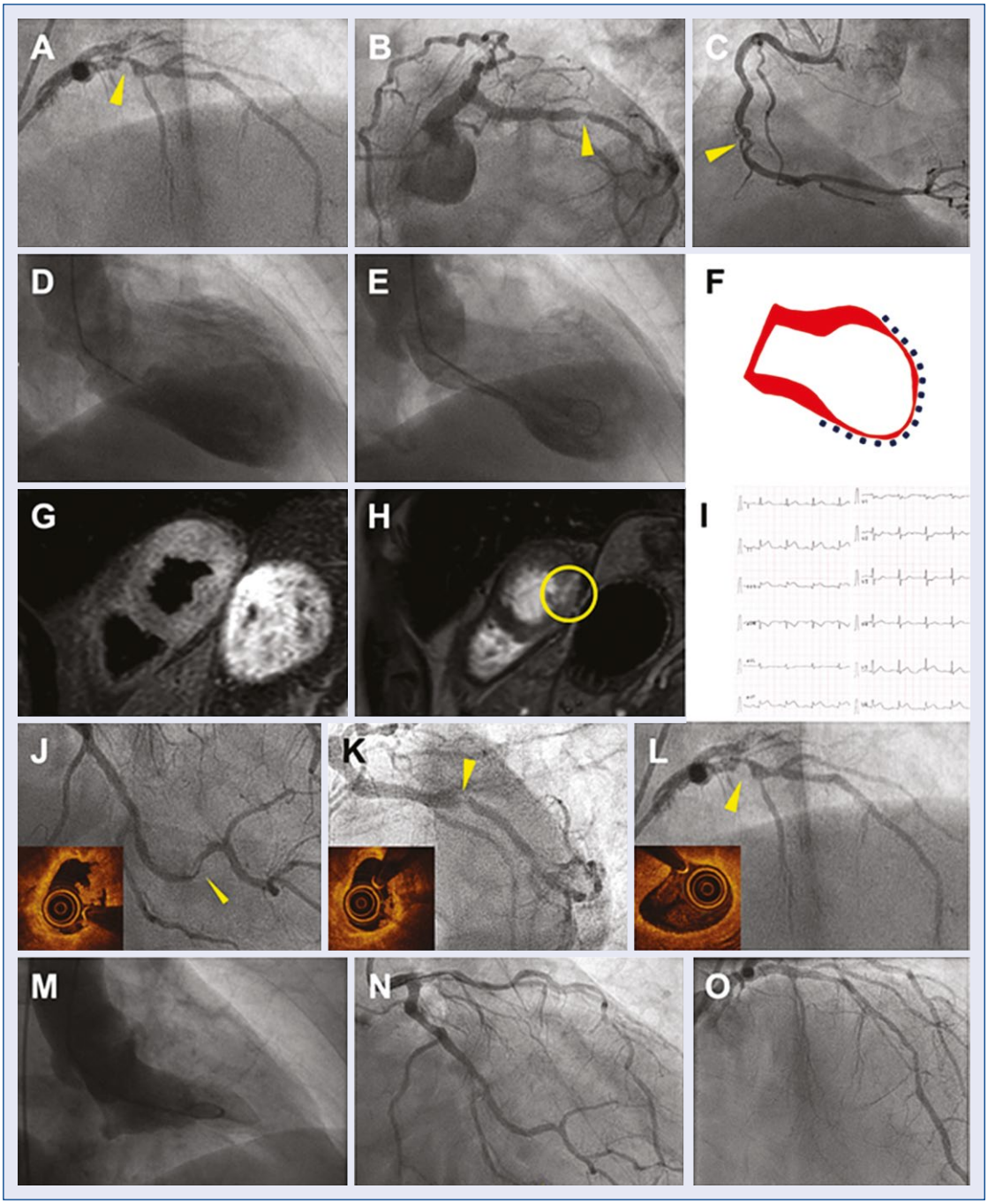

Figure 1. Coronary angiography showing three-vessel coronary artery disease with severe stenoses of the proximal left anterior descending artery (LAD) (**A**, arrowhead), the left marginal branch (**B**, arrowhead), and the mid-right coronary artery (**C**, arrowhead). Left ventriculography demonstrating akinesis of the midventricular and apical segments with normal contractions of the basal segments (**D**, **E**). Corresponding schematic of apical ballooning takotsubo syndrome (**F**, white: systole; red: diastole; blue dashed line: wall motion abnormalities). Cardiac magnetic resonance imaging, short axis, STIR sequence (T2-weighted) showing extensive edema of the midventricular segments (**G**). Cardiac magnetic resonance imaging, short axis, showing inferolateral late gadolinium enhancement (**H**, yellow circle). Electrocardiogram demonstrating ST-segment elevations in the inferior leads and V6 as well as ST-segment depression in V1–V3 consistent with infero-posterior ST-segment elevation myocardial infarction (**I**). Angiographic suspicion of an embolus in the distal left marginal branch (**J**, arrowhead) and evidence of thrombus on optical coherence tomography (OCT) (**J**, inset). Subtotal occlusion of the proximal left marginal branch (**K**, arrowhead) and evidence of thrombus on OCT (**K**, inset). Severe stenosis of the proximal LAD (**L**, arrowhead) without signs of plaque rupture, erosion, or thrombus on OCT (**L**, inset). Left ventriculography before staged percutaneous coronary intervention (PCI) of the LAD 1 month after the initial hospitalization demonstrating normalization of left ventricular function (**M**). Final result after PCI with stent implantation in the mid and distal part of the marginal branch (**N**) and in the proximal and distal part of the LAD (**O**).

tion myocardial infarction (STEMI) (Fig. 1I). By the time of immediate repeat coronary angiography, symptoms had resolved, and ST-segment changes had normalized. There was normal coronary artery flow in all three vessels. With the evidence of thrombus on optical coherence tomography (OCT) in the mid and distal part of the marginal branch (Fig. 1J and K, inset) it was considered that this vessel — rather than the RCA — is the culprit lesion of the actual STEMI and also of the initial NSTEMI with documented inferolateral scar on DE-CMR. Both lesions of the marginal branch were treated with implantation of a zotarolimus eluting stent (Resolute Onyx 2.5 mm × 12 mm proximal and 2.25 mm × 12 mm distal, Medtronic Inc., Minneapolis, MN, USA) (Fig. 1N). Furthermore, OCT was performed in the proximal LAD to rule out plaque rupture or plaque erosion as the cause of the apical ballooning (Fig. 1L, inset). Dual antiplatelet therapy was started with acetylsalicylic acid and ticagrelor.

A percutaneous approach was chosen for further revascularization of the remaining two-vessel disease due to patient preference and the distally diseased LAD being a suboptimal target for a coronary bypass graft. Based on the CMR and OCT findings, the proximal LAD stenosis was considered to be a stable lesion and it was assumed to be safer to delay revascularization for 1 month. Indeed, left ventriculography showed normalized LVEF by then (Fig. 1M) supporting the diagnosis of TTS. The stenoses in the proximal and distal LAD were treated with implantation of three stents (Resolute Onyx 3.5 mm × 15 mm, 2.5 mm × 22 mm and 2.25 mm × 15 mm) (Fig. 1O). After the patient developed shivering of unknown cause, planned revascularization of the RCA was not performed. A control DE-CMR did not show inferior ischemia and it was therefore decided to employ a conservative treatment.

The view herein, was that the most likely pathological mechanism in this case is a plaque rupture and infarction of the left marginal branch that triggered a TTS with reversible apical ballooning. ECG findings may support this sequence of events: while the ECG changes at presentation are more consistent with a marginal branch infarction, the widespread negative T-waves several hours later are more likely to have been caused by TTS, albeit T-wave inversions and their distribution in the present case are not specific for TTS or ACS [2].

Although exclusion of obstructive coronary artery disease was initially considered mandatory for the diagnosis of TTS, cases of TTS triggered by ACS have been reported, and may be underdiagnosed [3, 4]. In men, the prevalence of TTS is about 10 times lower than in women, while triggers are — as in our case — more often physical than emotional [5, 6].

This case represents a challenging clinical scenario in differentiating between ischemic and non-ischemic causes of NSTEMI on one hand, and identifying the culprit lesion in the context of three-vessel coronary artery disease on the other hand. Imaging with DE-CMR and OCT lead us to understand the case, and it is believed that the interplay between angiography and imaging modalities is critical to increase the diagnostic accuracy in NSTEMI patients.

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