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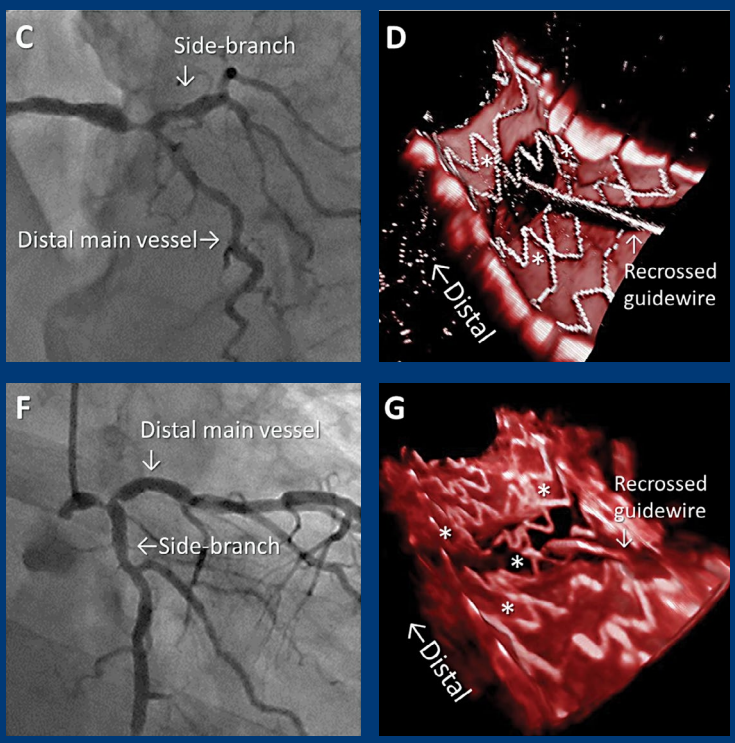

Fumiaki Nakao et al., see figure legend on page 207

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March 2019, Vol. 26, No. 2

Table of Contents

IMAGES IN CARDIOVASCULAR MEDICINE

Interventional cardiology

Clinical cardiology

BRIEF COMMUNICATION

Interventional cardiology

LETTERS TO THE EDITOR

Interventional cardiology

Clinical cardiology

VIA MEDICA

EDITORIAL

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The London PCHF: A new Postgraduate Course on Heart Failure

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The heart failure epidemic

Heart failure is a true medical epidemic for several reasons. Indeed, as societies age in the Western world, with long-standing high blood pressure in many individuals and the high survival rate of myocardial infarction thanks to effective interventional techniques, the prevalence and incidence of heart failure has continuously increased. This is associated not only with an impaired quality of life of the patients, but also with considerable costs for the health care systems and the society at large.

The main causes of heart failure are longstanding hypertension, arrythmias, coronary artery disease, mutations in genes of the contractile apparatus and valvular heart disease (Figure 1).

Increasing therapeutic options

Although, initially, heart failure was a condition with very unfavourable outcomes, recent developments of the management of such patients has markedly increased their longevity and reduced hospitalisations. Thanks to this medical progress today, cardiologists have many therapeutic options at hand, such as life style changes and rehabilitation, drugs, revascularisation with percutaneous coronary intervention or bypass surgery and valvular interventions, pacemakers and implantable cardioverter defibrillators (ICD), as well as cardiac resynchronisation therapy, and finally left ventricular assist devices (Figure 2). For selected patients, even heart transplantation may be an option.

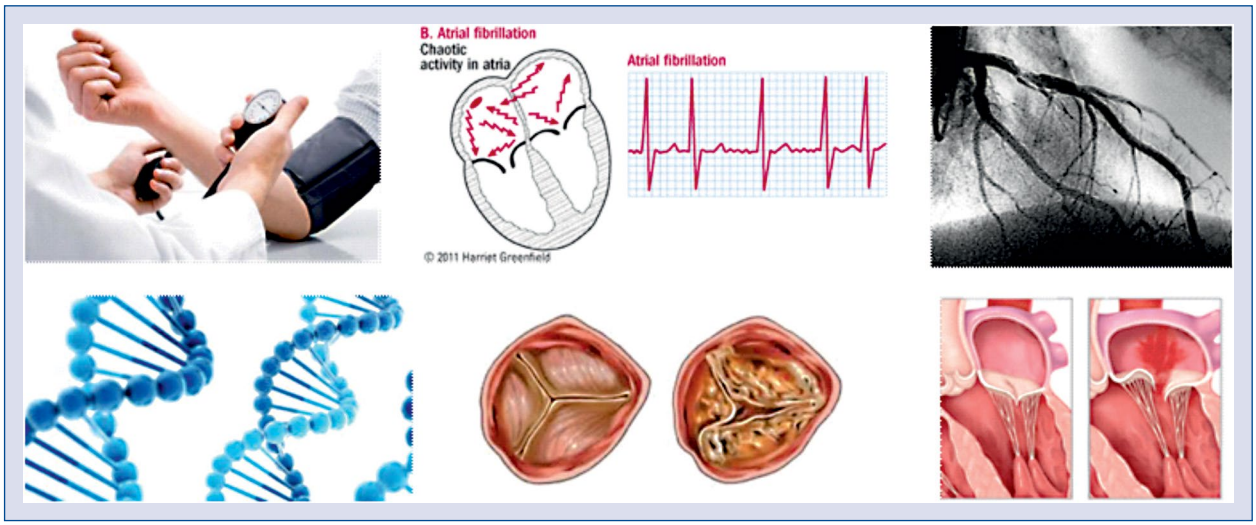

Figure 1. Most important causes of heart failure including hypertension, arrhythmias, coronary artery disease, genetics and valvular heart disease.

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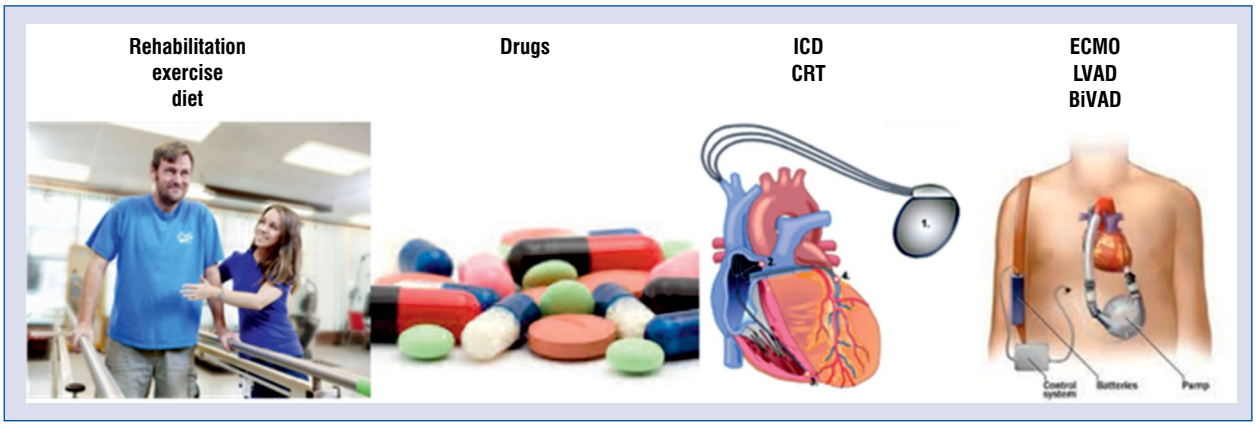

Figure 2. Therapeutic options in heart failure.

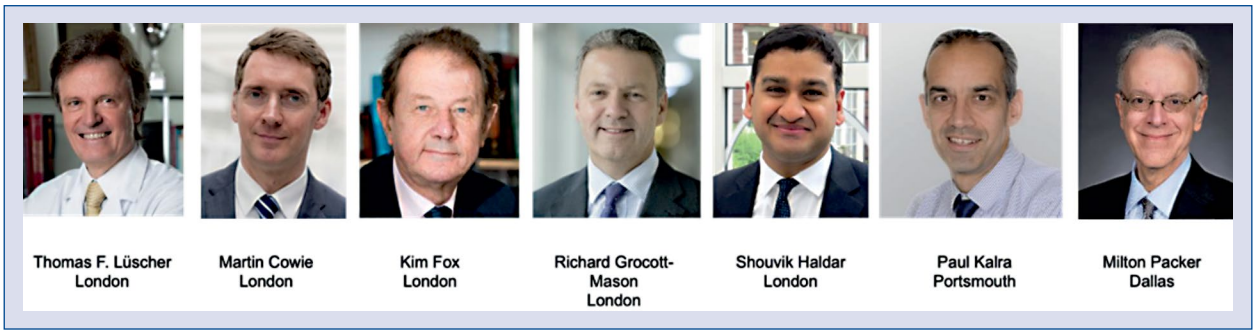

Figure 3. Directors of the London PCHF.

With these options the outcome of heart failure patients could be markedly improved both in reducing hospitalisations for heart failure and death.

Thus, heart failure doctors need an excellent training in all diagnostic and treatment modalities to properly take care of their patients.

The London PCHF

The new London Postgraduate Course in Heart Failure (*THE LONDON PCHF*), organised by the Royal Brompton and Harefield Hospitals and its *Institute for Medicine and Science* with support from the *British Cardiovascular Society* and the *British Society for Heart Failure* offers an educational programme at the highest academic and medical level. The experience and commitment of the *Zurich Heart House* and his educational team provides overall professional support for faculty and participants. The course directors are responsible for the content of the programme (Figure 3).

Course participants

The participants have been selected from close to 200 applicants by the Advisory Board of

Figure 4. Participants from Poland (from left to right): Michal Bohdan, Malgorzata Lelonek, Maria Niespialowska-Steuden (Credit J. Lipton)

the *London PCHF*. Eventually, 64 participants from 32 countries mainly from Europe, but also from the far east, South Africa and the Americas have been accepted. Of note, half of the participants each are of female and male gender. The requirements for application included a board certificate in cardiology (or shortly before it), interest in heart failure, pub-

Figure 5. Opening Session of the London PCHF with Bertram Pitt, Teresa McDonagh, Martin Cowie, John Cleland and Christian Mueller.

Figure 6. Paul Kalra discusses clinical cases in a breakout session (Credit J. Lipton).

lications on the topic and a recommendation letter by a supervisor. All 64 cardiologists participated in the first module that took place on January 16–19, 2019 at The Royal Society of Medicine, in Central London, as well as practical courses at the Royal Brompton and Harefield Hospitals, among them also three young cardiologists from Poland who were heardly welcomed (Figure 4).

Course structure

The course contains 6 modules of 4 days of lectures, interactive sessions, live transmissions and case presentations by the participants over a 2-year period.

The first module addressed the topic ***'How to Approach Heart Failure'*** chaired by Bertram Pitt from Ann Arbor, Michigan and began with lectures from eminent cardiologists such as Martin Cowie and Theresa McDonagh from London as well as Christian Mueller from Basle, Switzerland (Figure 5). The importance and assessment of heart failure was reviewed. These topics were further pursued in *Rapid Fire Sessions* (Figure 6) and presentations of challenging cases by the participants themselves. An important subject was the pathophysiology of heart failure reviewed by John Cleland from Glasgow, the haemodynamic changes and changes in the cardiac marker structure in such patients reviewed by Stephan Rosenkranz from Cologne, Germany.

Figure 7. Live demonstration of an ergospirometry by Luke Howard and Daniel Dumitrescu (Credit J. Lipton).

Figure 8. Hands-on echocardiography session at the Royal Brompton Hospital.

A highlight was a LIVE demonstration of an ergospirometry by both a pulmonologist and a cardiologist with an on-line transmission of the detailed oxygen metabolism as well as cardio-haemodynamic parameters (Figure 7). This was followed by another LIVE transmission by Roxy Senior and his team of a stress echocardiography with contrast, which impressively demonstrated the potential of this examination, if performed at such a professional level.

The first module was further complemented by lectures on comorbidities in heart failure by Christian

Angermann from Würzburg, Germany, diabetes and coronary artery disease and heart failure by Martin C. Petrie from Glasgow and finally on stunning and hibernation by Gerd Heusch from Essen, Germany.

Furthermore, diagnostic procedures such as left and right heart catheterisation and coronary angiography were demonstrated in impressive Live-in-a-box sessions by Stefan Rosenkranz and Ronald Binder from Wels, Austria.

For the assessment of patients with heart failure imaging technologies play a crucial role, as was outlined by highly educational lecture by Jeroen J. Bax, the former ESC President, on echocardiography and by Sanjay Prasad and Dudley Pennel from London on cardiac magnetic resonance imaging and Ronald Büchel from Zurich, on hybrid imaging to guide revascularisation in heart failure.

The Saturday part of the course focused on congenital heart disease with eminent lectures by Michael Gatzoulis, Andrew Bolger and Sonya Babu-Narayan followed by hands-on echo sessions, in small groups, at the Royal Brompton and Harefield Hospitals (Figure 8).

Thus, the London Postgraduate Course on Heart Failure started very successfully with happy participants and organizers and will continue in June with model 2, again at the *Royal Society of Medicine* in London.

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REVIEW ARTICLE

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Recommendations on the use of innovative medical technologies in cardiology and cardiac surgery and solutions leading to increased availability for Polish patients

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Abstract

There is a great need for innovative technologies that will improve the health and quality of life (QoL) of Polish patients with cardiac problems. It is important that the safety and effectiveness of the technology are confirmed by scientific evidence on which guidelines and clinical recommendations are based. Scientific evidence for medical devices is also increasingly important for decision-making in finance approval from public funds. New technologies in cardiology and cardiac surgery contribute to improved patient QoL, increased treatment effectiveness and facilitated diagnosis. Hence, it is necessary to increase accessibility to such technologies, primarily through the development of clinical recommendations, and education of medical personnel in conjunction with public funding. The aim of this publication is to present the recommendations of leading experts in the field of cardiology and cardiosurgery, supported by clinical research results, regarding the use of the cited innovative medical technologies and solutions leading to their increased availability for Polish patients. (Cardiol J 2019; 26, 2: 114–129)

Key words: coronary angioplasty, optical coherence tomography, heart failure, implantable loop recorder, mitral regurgitation, ventricular assist system, pulmonary artery pressure

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Introduction

New technologies in cardiology and cardiac surgery contribute to the improvement of quality of life (QoL) for patients by increasing the effectiveness of treatment and facilitating diagnostics. Therefore, if possible, striving to increase their accessibility primarily through the development of clinical recommendations, the education of medical personnel and public funding is paramount. Available guidelines of conduct, although very comprehensive, are constantly updated, and need to be supplemented in certain areas where innovative solutions can be applied.

Cardiovascular disease causes 45% of deaths in Poland (180,000 a year), while cancer comprises 26% of deaths. Due attention from a patient mortality perspective requires national health policy to be taken into account [1, 2]. There is, therefore, a great need for new innovative technologies that will improve the health and QoL of Polish patients with cardiac problems.

Unfortunately, the system at present significantly hinders the incorporation of innovative non-drug technologies into a basket of guaranteed services that has not adapted to medical progress. The costs of innovative medical technologies could be calculated in a new way. Nowadays, the cheapest procedures with immediate costs (direct) are chosen by the payer. However, additional costs, such as the cost of the treatment of subsequent complications, additional hospitalization and medicine, dismissal due to an inability to work, social welfare and sickness allowances and other costs are borne by a budget and patients are not taken into account. The choice of medical technology should be guided by an overall cost, and not just a greater temporary benefit through financing [3].

These recommendations are based on presentations and discussions that were held during Advisory Board meetings, which took place in cooperation with the 'Quo Vadis Cardiology?' initiative. Data collected during a questionnaire study which was conducted by the Arcana Institute are supported by clinical research results. The aim was to gather the opinions of leading experts (14 experts) in the field of conservative cardiology, interventional cardiology, electrophysiology and cardiac surgery for guidelines on the use of innovative medical technologies and solutions leading to increasing their availability for Polish patients.

The guidelines and recommendations presented apply to the following medical technologies:

- left ventricular assist systems/devices (LVAS/ /LVAD); e.g. HeartMate (HM) 3, HeartWare, BerlinHeart, TerumoHeart;
- a system for percutaneous repair of mitral regurgitation (MitraClip);
- a heart failure (HF) system for pulmonary artery pressure measurement (CardioMEMS);
- implantable loop recorders (ILR); e.g. Confirm Rx, Reveal DX and XT;
- optical coherence tomography (OCT).

Heart failure

Heart failure has become a realized epidemic of the 21 century. Almost 80% of cases result from coronary heart disease, which is accompanied by hypertension in 53% of cases. The remaining cases are the result of hypertension and other heart diseases. Heart disease has been a more frequent cause of death than cancer in Poland for many years (over 50% of deaths, amounting to approximately 60,000 deaths per year). This fact requires due attention when taking Poland's health policy into account [1, 2].

Currently, the number of patients at various stages of HF severity in Poland amounts to approximately 800,000 people [2]. Forecasts indicate that in 10 years this number will have increased by approximately 25%. A total of 60,000 people die each year due to HF and close to 150,000 are hospitalized [2]. HF hospitalization rates in Poland are among the highest in Europe (547/100,000 inhabitants) and unfortunately, despite the progress in treatment, the numbers have not changed significantly over the last 5 years (from 2008 to 2013). They are two times higher than in the Organization for Economic Co-operation and Development (OECD) countries and 5 times higher than in the United Kingdom. Total indirect costs of HF in Poland have been estimated to be approximately 4 billion PLN per year. Taking into account National Health Fund expenditure on treatment of HF at the level of approximately 900 million PLN in 2016, indirect costs of this disease in Poland are more than 4 times higher than direct medical costs [2]. This is primarily a consequence of the lack of effective medical technologies, not to mention a comprehensive model for patient care. HF is currently one of the largest unmet medical needs in Poland.

Methods of treatment

The treatment of HF aims to stop or reverse myocardial dysfunction, control symptoms and

reduce mortality. The choice of treatment depends on the type/cause of HF and clinical status of the patient [4]. If treatment options are exhausted, only heart transplantation (HTx) and mechanical circulatory support remain. HTx is currently one of the best methods of treatment of extreme HF, enabling long-term survival. Currently, the estimated annual survival for patients qualified for urgent cardiac transplant is < 50%, while after HTx, it is 50% over a 10-year period. Annually, approximately 5000 transplantations are performed worldwide, 2000 in the United States and nearly 1500 in Europe. The number of candidates for HTx is estimated to be 10 times higher. About 80–100 HTx are performed every year in Poland, while the demand is about 4 times higher [5]. The basic problem in transplantology is the limited number of organ donors. In addition, HTx is associated with a high frequency of appointments at an outpatient clinic and a long procedure. There is, therefore, an urgent need to look for other methods to support a damaged heart that would provide a longer survival time while waiting for HTx. The implantation of the ventricular assist system is a procedure that is performed in patients with severe and reversible (or irreversible) heart damage, in whom alternative treatment options have been exhausted, i.e. no other cardiac surgery is possible, and pharmacological treatment is not expected to stop further progression of the disease. Mechanical circulatory support devices are designed to support the work of the left (LVAD) or right (RVAD) ventricle. The use of ventricular assist device (VAD) was included in the 2016 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic HF (Fig. 1) [6].

Figure 1. HeartMate — left ventricular assist system (LVAS). This is the latest third generation pump (LVAD) with continuous blood flow, which is used for long-term cardiac support of patients suffering from severe heart failure as part of bridging therapy: for transplantation, for recovery or for candidacy/decision and as a target therapy. In the HeartMate 3 pump, the rotor is suspended in an electromagnetic field, thanks to which, the spaces which are not washed away by blood are removed and the occurrence of thromboembolic complications eliminated. A characteristic feature of this system is its ability to quickly change the flow rate (every 2 s), which can produce a rise of pulsation, or imitate natural blood flow.

Clinical evidence

Details about clinical evidence — see Table 1 [7–18].

Other methods of treatment and their comparison with HM3

— Other systems for mechanical circulatory support (MCS) — without 'artificial pulse' in comparison to HM3;
— External pump supporting the left ventricle and devices for extracorporeal oxygenation of the blood (ECMO) — disadvantages: no possibility of functioning at home, need for greater medical supervision:
  • HM3 — the complexity of supplying solutions to patients with HF — the possibility of waiting quietly for improvement of the left ventricular function or surgical treatment, the possibility of long-term use (also in an outpatient mode);
— Conservative treatment — disadvantages: higher frequency of appointments at an outpatient clinic, limited availability, longer duration of the procedure:
  • HM3 — greater patient survival.

Reimbursement and economic effectiveness

The economic analysis based on 2-year results from the MOMENTUM 3 study indicated that use of the HeartMate 3 pump reduced re-hospitalizations and the number of days for re-hospitalization and therefore contributed to a significant reduction in treatment costs compared to the HeartMate 2 pump [18].

In England, the expense is covered publicly and includes all the costs of providing the ser-

Table 1. Characteristics and main outcomes of clinical trials assessing the effectiveness and safety of HeartMate (HM). The conclusions of the REMATCH study led to the construction of a less faulty and a more durable cardiac pump, namely HeartMate 2 (HM2). Based on this study, the Food and Drug Administration adopted the indication for using the HeartMate left ventricular assist device (LVAD) pump as a target therapy. The results of the ROADMAP study indicated that the HM2 pump is better than optimal medical care (OMM) in terms of patient survival, the improvement in quality of life (QoL) and of class according to New York Heart Association (NYHA) classifications. ELEVATE is a post-marketing, prospective study based on the European registry for the first commercial use of the HeartMate 3 (HM3) pump, has demonstrated high clinical efficiency and good safety of HM3. The results of the MOMENTUM 3 study show the strength of the HM3 pump and support its use in patients with severe heart failure who are forced to wait a long time for transplantation or are not eligible for transplantation. In these patients, the HM3 pump can be used as a target therapy. The 2-year overall survival in MOMENTUM 3 was 82.8% for HM3 while in the case of heart transplantation (HTx), it is approximately 84%. Patient survival for both methods is currently comparable and of great importance considering the current organ donor shortage.

CHARACTERISTICS					
Study name	**Type of study**	**Population**	**Intervention**	**Comparator**	**Outcomes**
REMATCH [7, 8]	RCT	> 65 years old NYHA IV not eligible for HTx	HeartMate XVE	OMM	OS, QoL, median NYHA, adverse events
ROADMAP [9, 10, 11]	Observational	NYHA class IIIB/IV heart failure, with indications for LVAD but not dependent on intravenous inotropic drugs	HeartMate 2	OMM	Survival together with improvement in the length of a 6MWD ≥ 75 m after 12 months
ELEVATE [12]	Post-marketing, prospective study based on the European registry	Mean age: 56 years 48% ischemic etiology 70% inotropic 65% bridge to transplant 33% INTERMACS 1–2 38% INTERMACS 3 29% INTERMACS 4–6 8% ECMO	HeartMate 3	–	6MWD
MOMENTUM 3 [13, 14, 15, 16, 17, 18]	RCT	NYHA IIIB or IV Resistant to OMM	HeartMate 3	HeartMate 2	Stroke or reoperation to replace or remove the pump, free survival

→

	RESULTS						
Study name	**Overall survival**	**Event free survival**	**6MWD**	**QoL**	**Median NYHA**	**Change in NYHA**	**Adverse events**
REMATCH	**1-year:** 52% vs. 25% (p = 0.002) **2-year:** 23% vs. 8% (p = 0.09)	–	–	Better physical (p = 0.01) and emotional (p = 0.03) results, and depression was less frequent (p = 0.04)	**1-year:** II vs. IV	**HM2 group:** 25% change to class I; 52% change to class I **OMM group:** 0% change to class I; 29% change to class II	Incidence 2.35 times higher in HM group (most common: power cord infections leading to sepsis, bleeding and device failures)
ROADMAP	**1-year:** 80% vs. 63% (p = 0.022) **1-year with improvement in 6MWD:** 39% vs. 21% (p = 0.012) **2-year:** 70% vs. 41% (p < 0.001) **2-year with the improvement in 6MWD:** 30% vs 12% (p = 0.012)	–	–	PHQ-9: 5 vs. 1 (p < 0.001)			Incidence after 1-year: 1.89 times higher in HM2 group than OMM Most common: HM2 — bleeding; OMM — worsening of heart failure
ELEVATE	**1-year:** 74%	**–**	**1-year:** from 106 to 380 m	Significant increase of the patients QoL		82% NYHA I or II	Device thrombosis: 0.3% Serious bleeding: 29% Serious infection: 44% Stroke-type event: 8%
MOMENTUM 3	**2-year:** 82.8% vs. 76.2% (p = 0.16)	**6-months:** 86.2% vs. 76.8% (p < 0.001 for non-inferiority; p = 0.004 for superiority) (events: stroke or reoperation to replace or remove the pump) **2-years:** 77.9% vs. 56.4% (p < 0.001 for superiority)					Reoperation due to pump failure: 0.7% vs. 7.7% (p = 0.002) Pump thrombosis: 0% vs. 10.1%

6MWD — 6-minute walk distance; RCT — randomized clinical trial; ECMO — extracorporeal membrane oxygenation; OS — overall survival; INTERMACS — Interagency Registry for Mechanically Assisted Circulatory Support; PHQ-9 — Patient Health Questionnaire 9

vice, costs of hospitalization, diagnostic tests, medical devices and medicines. In Australia, services are provided as part of hospitalization are settled within the framework of the Diagnosis Related Groups (DRG) group funding system. A similar situation is present in New Zealand and Estonia. In Greece, funding is based on KEN-DRG groups (a combination of cost estimates from selected public hospitals and the 'imported' cost weight). In Germany, hospitalizations for the implementation of a cardiac support procedure are financed on the basis of the G-DRG system. In Croatia, under the public system, patients are required to pay 25% of the value of services provided as part of hospitalization and 40% of the value of services in an outpatient mode. The highest cost of implanting artificial chambers is observed in New Zealand, and the lowest, in Germany.

The cost of implanting artificial heart chambers, according to National Health Fund, ranges from 126,601 PLN to 375,207 PLN [19]. According to an analysis of impact on the organization of the healthcare system carried out by Agency for Health Technology Assessment and Tariff System (AOTMiT), financing the implantation of VAD pumps will result in a reduction of costs in this area. Potential savings will result from the fact that the patient treatment processes are conducted in outpatient mode at home, in contrast to patients treated with external pumps who are permanently hospitalized. Savings resulting from a reduction in medical costs could be allocated to other benefits. In addition, a comprehensive care model for patients with VAD can provide them with optimal supervision and treatment, which will certainly translate into an improvement of treatment results, the reduction of serious complications and mortality [4].

Expert recommendations

Experts indicated that using HM3 will contribute to an improvement in patient survival, QoL, treatment efficiency, the reduction of treatment costs and reduction in occurrence of adverse cardiovascular events.

Experts also pointed out that using HM3 will primarily affect not only a reduction in the number of patient hospitalizations, a reduction in additional procedures and diagnostic tests, but also a reduction in the need for medications. In Poland, approximately 100 heart pump insertions should be performed per year, which would satisfy the needs of patients. About 46 pumps are implanted every year in Poland (these are mainly HM3 pumps). The highest benefit from HM3 is received by patients in the INTERMACS 3 and 4 class. These are outpatients who stay at home and are not treated in hospital. These are also patients with normal right ventricle and no pulmonary hypertension, i.e. patients with a low risk of complications.

From the patient perspective using heart assist pumps as a target therapy is beneficial because it significantly improves QoL. The use of these pumps is important to the payer because it reduces the number of patient hospitalizations, procedures diagnostic tests, and additionally decreases the need for medicine. Periodical infections which occur due to using a power cord, may lead to a need for removal of the heart pump. In this case, the patient is referred for heart transplant. Therefore, an appropriate selection for a cardiac surgery center where cardiac transplants are performed requires recommendations for such an indication. Work is underway to construct a pump that will not require the use of an external power cord. In this case, implantation of this pump could be used as a target therapy.

Heart assist pumps should only be implanted in transplant centers. In this type of center, a full treatment profile should be available: all treatment options are in one place and comprehensive patient care is provided.

In Poland, the same services are performed during the implantation of a cardiac support pump as during HTx (a patient's qualification for the pump or transplant is the same). There is no procedure that would cover the cost of hospitalization after implantation of a heart pump. There is also a need to create a system for the comprehensive care for a patient with an LVAD.

In order to broaden patient access to HM3, experts first of all point to a need for adequate public funding, equipping clinical centers (apart from the technology itself) and increasing the level of awareness of the technology in the medical environment. The need for increased awareness about the availability of HM3 is also connected with a low level of awareness of this technology among physicians, especially primary care physicians. They mainly recommend drugs to young patients with HF, although they are eligible candidates for LVAD implantations.

Mitral regurgitation

Mitral regurgitation (MR) is currently the second most common valve defect in Europe [20]. The frequency of this defect increases with age and it is estimated that there are currently 2–2.5

Figure 2. MitraClip — a system for percutaneous repair of mitral regurgitation. The MitraClip system is used for percutaneous repair of mitral valve mitigation of the beating heart as an alternative to conventional cardiac surgery. The procedure is performed in a suitably adapted hemodynamic laboratory using transesophageal echocardiography and fluoroscopy [21]. The MitraClip system consists of an implant, an introductory catheter and an implant placement system that enables it to be placed on the mitral valve leaflet, causing it to be permanently approached, and a double-mitral valve is formed, thereby preventing blood from regressing. MitraClip is introduced into the mitral valve outlet via the venous system (femoral vein, inferior vena cava and then, after puncturing the atrial septum, to the left atrium) without opening the chest.

million people suffering from MR in the United States, and this number will double by 2030 due to an increase in size of the aging population [21]. The treatment of isolated mitral leaflet repair using the 'edge-to-edge' method was introduced in 1991 by Alfieri to repair prolapse of the anterior mitral leaflet [22]. The operation consists of sewing both mitral leaflets in the central part in order to increase contact of the anterior and posterior leaflets, which leads to a reduction of regurgitation. This technique is also useful in the loss of the posterior or both leaflets. A double orifice mitral valve, which is obtained through this procedure, does not usually cause narrowing of the mitral outlet, even in combination with annuloplasty, and, as a result, its surface area is reduced. This is the basis for the method of percutaneous treatment of MR (MitraClip) (Fig. 2) [21].

MitraClip is usually used to treat people with severe, post-infarction heart disease. In Europe, it is estimated that almost 1% of the population struggles with functional MR that results from a left ventricle defect after heart attacks or primary cardiomyopathy. In Poland, the figure amounts to approximately 400,000 people. Unfortunately, there are still far too few MitraClip procedures, due to a limited reimbursement by the National Health Fund. The MitraClip device reaches a price of approximately 80,000 PLN. However, the cost of long-term, repeated patient hospitalizations are comparable [23].

The MitraClip system has been used around the world since 2008. In Poland, only 9 centers perform procedures using MitraClip, which limits the frequency of this treatment in our country. A procedure using the MitraClip system, as a method of repairing heart valve leaflets, should be performed only at highly specialized centers.

Clinical evidence

Clinical trials have demonstrated the efficacy and safety of using MitraClip for percutaneous repair of MR. This was also confirmed on the basis of data from registers (Table 2) [24–28].

MITRA-FR, the first randomized, controlled trial of the percutaneous clip coaptation in degeneration of the mitral valve, showed no benefit of the MitraClip in addition to optimal medical care [29]. Over a 12-month period, 152 patients randomized to treatment with MitraClip experienced improvements of the MR grade and New York Heart Association (NYHA) class, but similar improvements were also seen in the 137 patients treated with optimal medical therapy. Over 12 months, the primary composite endpoint of all-cause death and unplanned re-hospitalization for HF had no significant difference between groups: 54.6% in the intervention group and 51.3% in the control group (odds ratio [OR] 1.16; 95% confidence interval [CI] 0.73–1.84). The limitation of the MITRA-FR study was that patients in the optimal medical care arm were not optimized before the trial, hence adjustments were performed after the trial had started.

The results of another randomized clinical trial, COAPT, in which 78 centers from the United States and Canada participated, showed a clear clinical efficacy of MR treatment with the use of MitraClip [30]. The COAPT trial is a United States Investigational Device Exemption, which was designed for Food and Drug Administration (FDA) approval of MitraClip for secondary MR. Patients with HF, in whom MR develops secondary to left ventricular dysfunction, have a poor prognosis, with reduced QoL, frequent hospitalizations due to HF and decreased survival. There are no proven therapies for secondary MR in HF. Guideline-directed medical therapy and cardiac resynchro-

Table 2. Summary of main results of studies and registries assessing efficacy and safety of the MitraClip system for percutaneous repair of mitral regurgitation [24]. In clinical trials and in medical practice (registry data), in patients with high operational risk (mean age 74–82), the MitraClip system for percutaneous repair of mitral regurgitation was associated with very high clinical efficacy (86–100%), which translated into an absence of death, cardiac surgeries or reoperations. The annual mortality after MitraClip implantation was low and ranged from 15% to 26%. In addition, the MitraClip system made it possible to achieve a low rate of hospitalizations due to heart failure within 1 year after surgery (7–23%) [24–28].

Study	Age [years]	DMR [%]	Acute success [%]	1-year mortality [%]	One-year HF hospitalization [%]
STS/ACC TVT	82	85.9	92.8	25.9	20.2
SENTINEL	74	28	95.4	15.3	22.8
ACCESS-EU	74	20.6	91.7	19.2	19.8
EVEREST II HRS*	76	29.9	86	22.8	–
EVEREST PR**	82	100	95.3	23.6	18
GRASP	72	23.9	100	16.2	7.1
TRAMI	76	93.8	97	20.3	14.1
MITRA Swiss	77	38	85	15.4	–

DMR — degeneration of the mitral valve, HF — heart failure; *HRS — high surgical risk cohort, **PR — percutaneous repair cohort

nization therapy may provide only symptomatic relief in some patients.

In this parallel-controlled, open-label, multicenter trial, 614 patients with HF and moderate-to-severe or severe secondary MR, who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy, were enrolled. Patients were randomly assigned to transcatheter mitral-valve repair (MitraClip) plus medical therapy (device group) or medical therapy alone (control group). The annualized rate of all hospitalizations due to HF within 24 months was 35.8% per patient-year in the device group, compared with 67.9% per patient-year in the control group (hazard ratio [HR] 0.53; 95% CI 0.40–0.70; $p < 0.001$). The rate of cases that were free from device-related complications at 12 months was 96.6% (lower 95% confidence limit, 94.8%; $p < 0.001$ for comparison with the performance goal). Death from any cause within 24 months occurred in 29.1% of patients in the device group compared with 46.1% in the control group (HR 0.62; 95% CI 0.46–0.82; $p < 0.001$). All-cause mortality within 24 months was significantly lower with device-based treatment than with medical therapy alone (29.1% vs. 46.1%; HR 0.62; 95% CI 0.46–0.82; $p < 0.001$). The number of patients needed to be treated to save one life within 24 months was 5.9 (95% CI 3.9–11.7) in the device group.

One possible reason for different outcomes between the MITRA-FR and COAPT studies was that in MITRA-FR, among the patients that were receiving HF medicines at baseline, variable adjustments in each group during a follow-up in comparison to 'real-world' practice was allowed. In the COAPT study, the Clinical Events Committee confirmed patients for whom maximally-tolerated guideline-directed medical therapy was not effective at baseline and there were few major changes during a follow-up. What is more, the procedural complications rate in MITRA-FR was almost 2 times higher than in the COAPT study (14.6% vs. 8.8%).

In this patient group, the use of MitraClip resulted in a lower rate of hospitalizations due to HF and lower all-cause mortality within 24 months of follow-up in comparison to medical therapy alone, while maintaining a very high rate of cases that were free from device-related complications [30]. As such, MitraClip was the first therapy that was shown to improve the prognosis of patients with HF by reducing secondary MR due to left ventricular dysfunction. Therefore, if MitraClip is the first-line therapy, it improves the prognosis of patients with HF by reducing secondary MR due to left ventricular dysfunction.

Reimbursement and economic effectiveness

As part of an economic analysis performed by AOTMiT, the use of MitraClip technology was compared with symptomatic pharmacological treatment as the only available therapeutic option in the target group of patients [31]. The results of the analysis indicated that the use of MitraClip tech-

nology provides better clinical effects compared to pharmacotherapy. Both the expected survival time and the quality-adjusted life years were prolonged. The ratio of additional costs to additional effects indicated that the use of MitraClip technology was cost-effective, i.e. it provided additional clinical effects at an acceptable additional cost. In a 10-year time horizon, the average cost of an additional year of life (when using MitraClip, compared to pharmacotherapy) is 36,502 PLN, and the average cost of an additional quality-adjusted year is 47,853 PLN, thus clearly below the profitability threshold (105,801 PLN).

Expert recommendations

In 2017, 140 treatment procedures were performed using the MitraClip system. However, this figure is still too low in relation to demand, while at the same time there is a continuous increase in the number of valvular interventions in Poland.

According to experts, there should be 10–20 centers that perform treatment with the use of MitraClip, this treatment includes refunds for patient transport to the center (declarations based on epidemiological data). Qualification and treatment should be carried out only at highly specialized centers.

Hemodynamic monitoring

Pulmonary artery (PA) pressure monitoring provides earlier detection of HF progression than other markers (i.e. patient weight, symptoms, blood pressure) [32]. PA pressure measurement, along with biochemical markers, have become the standard tools for managing all forms of HF. In combination with clinical symptoms, PA pressure measurement provides a rational basis for the choice of drug dosage.

The CardioMEMS system consists of an implantable wireless sensor with an introductory catheter, an electronic patient system, and a patient database for clinical review. The sensor is implanted using known catheter deployment methods and remains implanted for the rest of the patient's life. It does not have wires, generators or batteries which require replacement. The CardioMEMS system for pulmonary hemodynamic monitoring was approved by the FDA in 2014 and received a Conformité Européenne (CE) mark in 2011. It provides measurement of PA pressure non-invasively anytime and anywhere, enabling quick adjustments of therapy. A 15 × 3.5 mm CardioMEMS sensor is implanted into the lumen of the PA. Measurements are sent wirelessly via a transmitter, and the system is able to monitor PA pressure. The important thing to note is that the increase of intracardiac pressure and PA pressure precedes HF decompensation by several days. The PA CardioMEMS sensor provides non-invasive pressure data (PA waveform, systolic, diastolic, and moderate arterial pressure and heart rate). CardioMEMS provides direct PA pressure measurement and avoids the disadvantages associated with PA catheters and impedance measurements. Patients send information about daily pressure or as recommended, and this information is transmitted to a secure website. If the PA pressure exceeds set threshold values, clinicians are automatically informed.

CardioMEMS is indicated for patients with HF class III according to NYHA, who were hospitalized due to HF in the previous year. It is not recommended for patients who cannot take dual antiplatelet or anticoagulant medications for a month subsequent to PA sensor implantation.

The recommendation of the CardioMEMS system is included in the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic HF in symptomatic patients with HF, who had been previously hospitalized due to HF, thereby reducing the risk of rehospitalization (class IIb) [6].

Clinical evidence

Detail about clinical evidence — see Table 3 [33, 34].

Reimbursement and economic effectiveness

Currently, the CardioMEMS device is not financed from public funds in Poland. In clinical trials and on the basis of registry data in the United States, the use of the CardioMEMS system contributes to a significant reduction in the frequency of hospitalization and mortality, this directly translates into a reduction of costs associated with the treatment of HF [34].

Monitoring of heart rhythm disorders

Most cardiac arrhythmias can be diagnosed using standard ECG or Holter monitoring, but in some cases, arrhythmia is elusive and presently it was only suspected as a mechanism of the unconsciousness. Sometimes rhythm disorders occur so rarely that they cannot be predicted or triggered. In such cases, an ILR is required. The primary indication for ILR implantation is the diagnosis of syncope. It can also be used to differentiate heart palpitations of a symptomatic character that are rare: the records received enable a differentiation of sinus, ventricular and supraventricular tachycar-

Table 3. Characteristics and main outcomes of clinical trials assessing the effectiveness and safety of CardioMEMS. CardioMEMS is the first and only Food and Drug Administration-approved heart failure (HF) monitoring system that significantly reduces the number of HF hospitalizations and improves quality of life and physical performance. In clinical trials, the use of the CardioMEMS system for pulmonary artery (PA) measurement reduced hospitalizations by 33% over an average period of 18 months. CardioMEMS is an economical way to control the condition of patients with New York Heart Association HF class III. In Poland, work is currently underway to prepare for the first implantation of the device.

CHARACTERISTICS					
Study	**Study type**	**Population**	**Intervention**	**Comparator**	**Outcomes**
CHAMPION [33]	Randomized clinical trial	HF	CardioMEMS	No PA monitoring	Frequency of hospitalizations associated with HF
MEDICARE registry [34]	Real-world data	HF	CardioMEMS	–	Hospitalisation due to HF and mortality
Desai et al. [34]	Real-world data	HF	CardioMEMS	–	–

RESULTS			
Study	**Frequency of hospitalizations associated with HF**	**Mortality**	**Costs**
CHAMPION	**6-months:** 30% reduction compared to control **Observation period:** 39% reduction compared to control ($p < 0.0001$)	–	–
MEDICARE registry	24% reduction	1-year: 30% reduction	–
Desai et al.	5 months: 45% reduction		Significant reduction in costs associated with HF treatment

dias. ILR can also be used to monitor heart rhythm in patients before and after ablation treatment due to atrial fibrillation. The use of ILR is indicated in the ESC Guidelines:

— 2009 and 2018 — regarding the diagnosis and management of syncope [35, 36];
— 2015 — concerning the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death [37];
— 2016 — for the treatment of atrial fibrillation [38].

In the latest ESC Guidelines from 2018, indications for the use of ILR have been extended to patients [36]:

— with suspected anecdotal epilepsy;
— who experience unexplained falls;
— with primary cardiomyopathy or inherited arrhythmogenic disorder, who are at low risk of sudden cardiac death, as an alternative to implantable cardioverter-defibrillator (ICD).

The new guidelines emphasize the role of long-term diagnosis in the absence of a documented cause of syncope, and ILR value has gained a new class of indications, namely IA.

Confirm Rx is an under-the-skin implantable long-lasting heart rate recorder, which is currently the only one in the world with Bluetooth technology. Thanks to this, it connects directly to the patient's smartphone, which eliminates the need for a handy event recorder and a stationary transmitter. Through this technology, the recording of an abnormal heart rhythm can be immediately sent to the central control system, where data are stored and then analyzed by a doctor, who takes appropriate action depending on the cause of the symptoms. The advantage of Confirm Rx is the small size of the device (the pursuit of miniaturization) and only a few dozen seconds of procedure, which makes it possible to implant the device in a treatment room. The procedure is carried out in the subcutaneous area and enables long-term diagnostics. Confirm Rx is the simplest and easiest to implant device among the devices of this type available on the market.

The first ILR implantation in Poland was carried out in 2015 (it was not Confirm Rx but another device, without Bluetooth technology) [39]. The first implantation of the Confirm Rx recorder in a child recently has been done. Such devices are

currently not reimbursed in Poland. Confirm Rx is currently under reimbursement procedure in France. In Germany, mHealth (mobile health — services related to telemedicine) have independent funding. Many countries, including the United States, are implementing a procedure to increase the availability of this technology for their patients.

Clinical evidence

The location of ILR devices in the ESC Guidelines and the widening of the indications for their use has support in the results of many randomized clinical trials showing a significant advantage of ILR over standard diagnostics. In a meta-analysis of 5 randomized clinical trials, which are presented in the ESC 2018 Guidelines on diagnosis and management of syncope, 660 patients with unexplained syncope were randomized to standard management (external loop recorders, incline test, electrophysiological study) or extended monitoring with ILR [36]. The result showed that the use of ILR increased by almost 4 times the chance of diagnosing unexplained cases of syncope compared to the standard procedure (relative risk [RR]) 3.7; 95% CI 2.7–5.0; p = 0.001). Statistical analysis carried out by the authors of the study showed the statistical significance of the results obtained. In patients with a bundle branch block in whom the atrioventricular block is likely to occur despite a negative complete electrophysiology study, arrhythmia was observed in 41% of these patients (70% atrioventricular blocking) due to ILR monitoring, based on a pooled analysis from 3 clinical trials [36]. In patients who were suspected of epilepsy, but treatment turned out to be ineffective, results of a pooled analysis of clinical trials showed that the attack was documented by ILR in 62% of patients, with 26% of the patients in whom it was caused by arrhythmias [36]. Among patients with unexplained falls, the results from a pooled analysis of clinical trials showed that the attack was documented by ILR in 70% of patients, with 14% of patients in whom it was caused by arrhythmia.

Other diagnostic methods used to monitor heart disorder and their comparison with Confirm Rx™

- Other subcutaneous implantable recorders (Reveal, BioMonitor 2):
  - CRx — additional features, e.g. Bluetooth communication;
- Telemonitoring/smartphone applications connected with an external device:
  - CRx — possible diagnosis of the type of arrhythmias (similar to a pacemaker);
- Electrocardiography:
  - CRx — usually makes it possible to give a final diagnosis;
- External recorders (including loop):
  - CRx — independent from patient, long-term, constant monitoring; diagnostic efficiency;
- Holter;
- Implantable pacemakers and defibrillator (ICD).

Reimbursement and economic effectiveness

These devices, which are used to detect asymptomatic arrhythmias and conduction disorders, are not currently reimbursed in Poland. Confirm Rx is currently under reimbursement procedure in France. In Germany, mHealth (mobile health — services related to telemedicine) have independent funding. Most countries, including the United States, are implementing a procedure to increase the availability of this technology for their patients.

In a randomized clinical trial of syncope assessment ('Cost Implications of Testing Strategy in Patients with Syncope'), it was concluded that a strategy of prolonged monitoring with implantable recorders is a more cost–effective and efficient diagnostic approach than conventional testing in patients with recurrent, unexplained syncope and preserved left ventricular function. The strategy of primary monitoring significantly reduced the cost by $2016 (p = 0.002) [40].

In a randomized study in the early use of an ILR syncope evaluation (FRESH study), it was concluded that in patients with unexplained syncope, the early use of an ILR had a superior diagnostic yield in comparison to the conventional strategy, with lower healthcare-related costs [41].

In a randomized Diamantopoulos 2016 study, it was concluded that insertable cardiac monitors are a cost–effective diagnostic tool for the prevention of recurrent stroke in patients with a cryptogenic stroke [42].

In a randomized Giada 2007 study, despite the higher initial cost, the cost per diagnosis in the ILR group was lower than in the conventional strategy group (€3056 ± €363 vs. €6768 ± €6672, p = 0.012) for diagnosis of recurrent unexplained palpitations [43].

In a Davis 2012 study, ILR monitoring was found to be a likely cost–effective strategy for patients in the United Kingdom National Health

Service, who had experienced infrequent episodes of transient loss of consciousness, which had either remained unexplained or were suspected to be of arrhythmia-origin after an initial assessment and specialist cardiovascular assessment [44].

Expert recommendations

The indication of experts on groups of patients who would benefit from the use of Confirm Rx, are in line with the ESC Guidelines. The majority of experts also indicated that the use of Confirm Rx would contribute to improved diagnoses of the disease, patient safety, treatment efficiency, reduction in the frequency of appointments/hospitalizations, treatment costs and occurrence of adverse cardiovascular events (including stroke and sudden cardiac death). In order to broaden patient access to Confirm Rx, experts primarily pointed to financing of the technology from public funds and development of recommendations for use of this technology.

Methods of intravascular imaging

Optical coherence tomography is an intravascular visualization method based on the reflection of an infrared light beam, which has been used in interventional cardiology since the beginning of this century. This method is characterized by high resolution, up to 10 times higher than intravascular ultrasound (IVUS). It provides faster and longer image acquisition (compared to IVUS) and co-acquisition with angiography. Thanks to OCT, the accurate assessment of bifurcation and atherosclerotic plaque, thrombus diagnosis, early analysis of angioplasty effects, analysis of restenosis and optimization of percutaneous coronary intervention (PCI) surgery are possible. It also provides three-dimensional reconstruction of blood vessels.

The recommendation on the use of OCT is included in the ESC Guidelines:

— 2013 — regarding the management of stable coronary heart disease [45];
— 2014 — concerning myocardial revascularization [46];
— 2018 — concerning myocardial revascularization [47].

In current European clinical practice guidelines from 2018, OCT is recommended for stent optimization and was moved from class IIb to class IIa; e.g., OCT should be considered in the detection of stent-related mechanical problems, which lead to restenosis (class IIa) [47].

In the latest ILUMIEN OPTIS apparatus, which is used for intravascular imaging, the OCT method was integrated with the fractional flow reserve method. The integration of both methods in one platform enables the combination of two techniques to optimize coronary angioplasty procedures in 1 patient. Due to the increase of frequency, it became possible to significantly accelerate the operation of the pull-back device in the system and significantly reduce the amount of contrast administered to the coronary artery. Owing to the small diameter of the Dragonfly catheter, it is possible to visualize tight changes in the coronary arteries. The axial resolution is only 15 μm with 10 mm penetration of the light beam. The fractional flow reserve measurement module in the system operates in a wireless mode, thanks to which it can be used in many cardiac laboratories without the need for complicated installations [48].

Clinical evidence

The predominance of intravascular imaging with OCT over IVUS and angiography during PCI has been confirmed in clinical trials (Table 4) [49–50].

Other methods of intravascular imaging

Other methods of intravascular imaging including:

— magnetic resonance;
— coronary angiography;
— scintigraphy;
— thermography (experimental).

Patient groups and indications in which the use of OCT will provide the greatest benefit:

— young patients with unstable angina and border atherosclerotic lesions;
— patients with left main trunk disease and/or the disease of major coronary vessels;
— the assessment of the causes of thrombosis/restenosis;
— the optimization of stent implantation (e.g. left coronary artery stump, bifurcations) — the ambiguous results of angiography, e.g. suspected thrombus, calcifications;
— the evaluation of atherosclerotic plaque;
— the evaluation of the effectiveness of PCI and stent apex.

Patient groups and indications in which the use of OCT will provide a potential benefit (in addition):

— the diagnosis of acute coronary syndrome (including acute coronary syndrome without critical lesions, myocardial infarction (STEMI/NSTEMI, MINOCA) — the assessment of morphology of atherosclerotic lesions (dif-

Table 4. Characteristics and main outcomes of clinical trials assessing the effectiveness and safety of optical coherence tomography (OCT).

CHARACTERISTICS							
Study		**Study type**	**Population**	**Intervention**	**Comparator**		**Outcomes**
CLI-OPCI [49]		Retrospective	Patients undergoing PCI	Imaging using angioplasty supported by OCT	Imaging using angioplasty		The incidence of cardiac death or MI after 1 year following surgery
ILUMIEN III [50]		RCT	Patients undergoing PCI	Imaging using OCT	Imaging using angiography or IVUS		Minimum stent area
RESULTS							
Study	**Diagnosis of PCI-related abnormalities**	**Risk of cardiac death**	**Risk of heart death or MI**	**MI or re-revascular-ization**	**Minimum stent area**	**Dissemination of the vessel**	**Incorrect stent placement**
CLI-OPCI	34.7% by OCT	1.2% vs. 4.5% ($p = 0.010$)	6.6% vs. 13% ($p = 0.006$)	9.6% vs. 14.8% ($p = 0.044$)	–	–	–
ILUMIEN III	–	–	–	–	5.79 mm^2 vs. 5.89 mm^2 (IVUS) vs. 5.49 mm^2 (angiography) ($p = 0.0014$ for non-inferiority vs. IVUS)	13.6% vs. 26.1% (IVUS) ($p = 0.091$)	More frequent using IVUS ($p = 0.022$) and angiography ($p < 0.001$)

IVUS — intravascular ultrasound imaging; MI — myocardial infarction; PCI — percutaneous coronary intervention; RCT — randomized clinical trial

ferentiation between atherosclerotic plaque rupture and atherosclerotic plaque erosion, the diagnosis of unstable/atherosclerotic plaques);
— coronary heart disease (the evaluation of coronary lesions);
— the unclear results of coronarography;
— bifurcation.

Expert recommendations

Experts have indicated that the use of OCT will primarily affect the reduction of the number of diagnostic tests and additional procedures. It will also contribute to improvements in the diagnosis of the disease, patient safety, treatment efficiency, the reduction of treatment costs, the occurrence of adverse cardiovascular events and the improvement of the quality of interventions on coronary vessels.

Experts stated that patients have better results after OCT-assisted vs. non-assisted intervention (similar conclusions for IVUS). At present in Poland, OCT is only reimbursed in ophthalmology, however, experts have indicated that in cardiology OCT should be reimbursed and be equally as available as IVUS. This technology is reimbursed in most European Union countries. Both methods should therefore be the technologies to be used by choice, based on the operator's decision. In order to broaden patient access to OCT, experts mainly pointed out recommendations for using this technology, obtaining financing from public funds and increasing the number of centers that use this technology.

Conclusions

The aim of this publication is to present the recommendations of leading experts in the field of cardiology and cardio-surgery, which are supported by clinical research results, regarding the use of cited innovative medical technologies and solutions that lead to an increase of their availability for Polish patients.

When considering the country's health policy in Poland, diseases of the cardiovascular system requires due attention given that they are an even more frequent cause of death than cancer. There is a great need to introduce new innovative technologies to improve health and QoL of Polish patients with cardiac problems. These are not only medical technologies that can be further used directly in the treatment of patients (LVAD, e.g.: HeartMate 3; the system for percutaneous repair of MR: MitraClip), but also diagnostic technologies that enable faster and more effective detection of the disease (ILR, e.g. Confirm Rx, PA pressure measurement systems: CardioMEMS) or increase the effectiveness of treatment (OCT). The safety and effectiveness of the described technologies have been confirmed in numerous scientific studies, not only in randomized clinical trials, but also in observational studies subsequent to the introduction of the technology into medical practice. Both guidelines and clinical recommendations can be based on this evidence. Scientific evidence for medical devices is also increasingly important for making decisions about their financing from public funds. The use of the above-mentioned technologies also affects a reduction in the number of additional medical services, namely the number of hospitalizations, the reduction in the quantity of diagnostic tests or the demand and use of medicines, which can directly translate into a reduction of costs. Currently, the largest obstacle to the introduction of innovative health technologies is a lack of public funding, an incorrect calculation of costs associated with individual technologies and a system that hinders the incorporation of innovative non-drug technologies into a guaranteed benefit package.

New diagnostic and therapeutic technologies in cardiology and cardiac surgery contribute improvement in patient QoL and an increase treatment effectiveness. The use of these technologies also reduces direct costs, such as drug use, additional diagnostic tests and indirect costs such as additional hospitalizations, absence from work or permanent inability to work. It is therefore necessary to increase their availability, primarily through the development of clinical recommendations, education of medical personnel and public funding.

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Mechanical efficiency of high versus moderate intensity aerobic exercise in coronary heart disease patients: A randomized clinical trial

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Abstract

Background: *Mechanical efficiency (ME) refers to the ability of an individual to transfer energy consumed by external work. A decreased ME, could represent an increased energy cost during exercise and may, therefore, be limited in terms of physical activity. This study aimed to compare the influence of two different exercise protocols: moderate continuous training (MCT) versus high intensity interval training (HIIT), as part of a cardiac rehabilitation program on ME values among coronary patients.*

Methods: *One hundred and ten coronary patients were assigned to either HIIT or MCT groups for 8 weeks. Incremental exercise tests in a cycle ergometer were performed to obtain VO_2peak. Net energy expenditure (EE) and ME were obtained at intensities corresponding to the first (VT_1) and second (VT_2) ventilatory thresholds, and at VO_2peak.*

Results: *Both exercise programs significantly increase VO_2peak with a higher increase in the HIIT group (2.96 ± 2.33 mL/kg/min vs. 3.88 ± 2.40 mL/kg/min, for patients of the MCT and HIIT groups, respectively, $p < 0.001$). The ME at VO_2peak and VT_2 only significantly increased in the HIIT group. At VT_1, ME significantly increased in both groups, with a greater increase in the HIIT group (2.20 ± ± 6.25% vs. 5.52 ± 5.53%, for patients of the MCT and HIIT groups, respectively, $p < 0.001$).*

Conclusions: *The application of HIIT to patients with chronic ischemic heart disease of low risk resulted in a greater improvement in VO_2peak and in ME at VT_1, than when MCT was applied. Moreover, only the application of HIIT brought about a significant increase in ME at VT_2 and at VO_2peak.* (Cardiol J 2019; 26, 2: 130–137)

Key words: coronary artery disease, cardiopulmonary exercise test, high interval training, mechanical efficiency, energy expenditure

Introduction

Mechanical efficiency (ME) refers to the ability of an individual to transfer energy consumed by external work. Most studies that assess the efficiency of the different cardiac rehabilitation exercise programs evaluate the modification of the cardiovascular risk factors, quality of life and clinical variables associated with the prognosis of morbidity and mortality (i.e. VO_2peak), but there

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is very little research that evaluates ME, even though it provides important information concerning biomechanical adaptations and the use of the energy sources associated with clinical training and therefore the functional capacity of patients.

A decreased ME, which indicates that more energy is consumed at a given work output, could represent an increased energy cost of breathing during exercise, an altered efficiency in ATP production (ATP produced per O_2 consumed), or a higher ATP cost of contraction (ATP consumed per work output) [1]. Therefore, individuals with lower ME values should be less efficient in respect to performance and may therefore be limited in terms of physical activity [2]. Consequently, the evaluating ME may be valuable for the detection of muscle dysfunction and the assessment of any subsequent adaptations in response to training [3].

The results of a recent meta-analysis [4] have confirmed that the inclusion of exercise programs in cardiac rehabilitation reduces cardiovascular mortality and hospital readmissions in coronary artery disease (CAD) patients. For many years moderate continuous training (MCT) has been accepted as the gold standard [5]. However, recent evidence suggests that high intensity interval training (HIIT) may be a better modality for the improvement of aerobic exercise capacity [6]. Recently, with CAD patients, a superiority has been demonstrated of HIIT over MCT with greater increases in VO_2peak, as well as the recuperation rates of post-exercise heart rate. This constitutes an emerging prognostic variable of heart disease [7, 8].

Several studies have demonstrated that HIIT results in significant increases in muscle performance in untrained males. These adaptations are likely the result of skeletal muscle adaptations related to metabolic improvement associated with strengthening of muscle. Given that metabolic environment and muscle function may condition muscle performance and muscle energy profile of an individual, it is possible that any improvement in these parameters may be predictive of a subsequent increase in ME [2]. Therefore, ME may also be an important predictor of efficacy and may provide relevant data regarding performance and energy use adaptations in response to training [2].

Studies in young adults and older individuals [3] have reported significant increases in ME in response to HIIT. Considering that HIIT demonstrated a multitude of physiological adaptations that were correlated with performance and health benefits [9, 10], it was hypothesized that this form of exercise may promote greater improvements in ME among CAD patients.

This study aimed to compare the influence of two different exercise protocols (MCT vs. HIIT) as part of a cardiac rehabilitation program on ME values among coronary patients.

Methods

Study population

This is a unicentric, prospective and randomized clinical trial in patients with stable CAD, which was registered on clinicaltrials.gov (NCT02168712). All patients underwent exercise testing with a cycle ergometer including analysis of exhaled gases.

The main study inclusion criteria were: 1) Stable New York Heart Association functional class I or II CAD with angina pectoris or myocardial infarction and no heart failure; 2) No change in medication during the study; 3) Included between 6 and 12 weeks following the cardiac event, elective percutaneous coronary intervention, or coronary artery bypass grafting; 4) Achieve the first (VT_1) and second (VT_2) ventilatory thresholds in the initial and final (cardiopulmonary exercise test [CPET]) and 5) Achieve a respiratory exchange ratio $\geq$ 1.10 in both CPET. Patients who had residual ischemia (by electrocardiogram criteria or angina symptoms), severe ventricular arrhythmias, uncontrolled hypertension, permanent pacemakers, or implanted cardiac defibrillators were excluded.

Patients were randomized on a one-to-one basis to either the MCT or the HIIT group. The mode of exercise training was a cycle ergometer with 40 min per session, 3 days per week (total of 24 sessions over 2 months).

Selected CPET variables and ME measurement were recorded before and after the exercise program. ME (expressed as a percentage) was calculated during an incremental maximal cycling test at stages corresponding to VT_1, VT_2 and VO_2peak. CPET were administered by staff who were unaware of the exercise training group the patients were assigned.

The study complies with the Declaration of Helsinki and was approved by the Local Ethics Committees, and written informed consent was obtained from each participant.

Characteristics and medication use of the patients are shown in Table 1.

Cardiopulmonary exercise test

The test was performed on an electro-mechanically braked cycle ergometer (Ergoline900S). The cycling position, which is known to affect

Table 1. Patient characteristics and medication use.

	MCT (n = 53)	HIIT (n = 57)	P
Age [years]	58.3 ± 9.5	57.6 ± 9.8	0.752
Men	42 (79.2%)	50 (87.7%)	0.234
Body mass index [kg/m^2]	27.8 ± 3.7	29.1 ± 3.9	0.909
Waist circumference [cm]	98.7 ± 8.9	101 ± 14.3	0.879
Hip circumference [cm]	102.1 ± 6.8	103.5 ± 8.1	0.353
Cardiovascular risk factors:	3.9%	11.3%	
Family history	47.2%	42.1%	0.743
Hypertension	47.1%	49.1%	1.000
Diabetes mellitus	24.5%	25.4%	1.000
Dyslipidemia	52.8%	58.8%	0.743
Smoking	73.6%	82.3%	0.754
Stroke	5.6%	3.5%	1.000
Peripheral vascular disease	7.8%	5.7%	1.000
Hyperuricemia	3.9%	11.3%	1.000
Heart disease factors:			
LVEF [%]	60.3 ± 9.7	61.2 ± 10.1	0.622
Intervention:			
Conservative	9.4%	8.8%	1.000
PCI	79.3%	82.4%	0.531
CABG	11.3%	8.7%	0.429
Drugs administered:	21.6%	20.7%	
Beta-blockers	90.1%	86.8%	1.000
Calcium channel blockers	13.2%	19.3%	0.684
ACE-inhibitors	88.2%	81.1%	0.897
Angiotensin receptor antagonists	17.6%	16.9%	1.000
Nitrates	15.6%	7.5%	0.497
Antiplatelet agents	97.3%	97.4%	1.000
Acenocoumarol	9.4%	5.4%	0.596
Statins	96.7%	100.0%	0.828
Ezetimibe	5.6%	5.3%	1.000
Antidiabetics	21.6%	20.7%	1.000

ACE — angiotensin converting enzyme; CABG — coronary artery bypass graft; HIIT — high-intensity interval training; LVEF — left ventricular ejection fraction; MCT — moderate continuous training; PCI — percutaneous coronary intervention

energy expenditure, was standardized by adopting a top bar position. Saddle height was adjusted according to the participant's leg length and knee flexion was between 20 and 30 degrees. Toe-clips were used and participants were instructed to stay seated during the test. Patients were required to maintain a constant pedal cadence between 50 and 70 revolutions per minute.

An individualized exercise protocol was performed in all patients and was tailored to each patient's physical condition, with gradual increments of 10, 15, or 20 W/min. Required exercise time was between 6 and 12 min in order to respect the proper kinetics of oxygen consumption (VO_2) and to maintain a linear relationship between VO_2, exercise workload and heart rate (HR) during CPET. The same protocol was applied before and after the exercise training program. Throughout the test, patients were kept under continuous 12-lead electrocardiographic-monitoring, and blood pressure was established every 3 min.

VO_2 was determined breath by breath using an automated system (UltimaCardiO2, Medical GraphicsCorporation, St. Paul, Minnesota, USA). The gas analysers were calibrated before each test.

Table 2. Program designs for moderate continuous training (MCT) group or high intensity interval training (HIIT) group.

Week	Warm-up time and intensity (MCT and HIIT)	Exercise time and intensity	Cool-down time and intensity (MCT and HIIT)
1	12 min (25 watts)	MCT: 15 min at VT_1	13 min (25 watts)
		HIIT: 15 repetition (*)	
2	10 min (25 watts)	MCT: 20 min at VT_1	10 min (25 watts)
		HIIT: 20 repetition (*)	
3	7 min (25 watts)	MCT: 25 min at VT_1	8 min (25 watts)
		HIIT: 25 repetition (*)	
4	5 min (25 watts)	MCT: 30 min at VT_1	5 min (25 watts)
		HIIT: 30 repetition (*)	
4–8	5 min (25 watts)	MCT: 30 min at VT_1 + 10%	5 min (25 watts)
		HIIT: 30 repetition (**)	

*20-second repetitions at 50% of the maximum load reached with the first steep ramp test (SRT) followed by 40-second of recovery period at 10% of the first SRT; **20-second repetitions at 50% of the maximum load reached with the second SRT followed by 40-second of recovery period at 10% of the second SRT; VT_1 — first ventilatory threshold

The VT_1 and VT_2 were determined following the method of ventilatory equivalents described by Skinner et al. [11]. VT_1 corresponds to an increment of the VE/VO_2 ratio without an increased VE/VCO_2 ratio, and with an increased concentration of oxygen fraction ($PetO_2$). VT_2 corresponds to an increment of the VE/VCO_2 ratio and a fractional decrease in the concentration of CO_2 ($PetCO_2$).

Training interventions

MCT-Program Designs. To design the intensity prescription in MCT-program, the HR reached at VT_1 were used and obtained during the pre-training CPET. During the second month, the intensity of the exercise was adjusted, increasing to a training HR that corresponded to VT_1 plus 10% [7, 8].

HIIT-Program Designs. To design the HIIT-program, the steep ramp test (SRT) protocol was used according to the methodology described by Meyer et al. [12] and described by the present work group in several articles [7, 8]. The maximum exercise load achieved (watts), was the exercise parameter used to design the HIIT-program for each patient. In the first month of training, 20-s repetitions at an intensity corresponding to 50% of the maximum load reached with the SRT (peak intervals) were followed by 40-s recovery periods at 10%. In the second month of training, the intensity of exercise was adjusted using the results of a new SRT.

The total duration of both modalities of training was 40 min per session throughout the exercise program (including warm-up and cool-down). Table 2 summarizes the exercise time and intensity progression for both MCT and HIIT. Patients enrolled in the study participated in other activities established in this cardiac rehabilitation program that were aimed at managing psychological stress and learning about cardiac health habits. They were also taught to devise a home walking program for the days on which they did not have to attend sessions in the hospital. The recommended intensity of walking was a perceived exertion of 11 to 13 on the Börg Scale.

Energy consumption and mechanical efficiency calculations

VO_2net was obtained by subtracting resting VO_2 from total VO_2 at each exercise stage. The net energy expenditure (EE) in watts was calculated as follows [13]: $(4.94 \times RER + 16.04) \times (VO_2net, \text{ in mL/min}) \times 60^{-1}$. ME was also calculated in net terms as follows [14]: work produced in Watts × (EE net, in $Watts^{-1}$) × 100^{-1}. EE and ME were obtained at intensities corresponding to VT_1, VT_2 and at VO_2peak. This method allowed a comparison of these variables in terms of relative exercise intensity [3].

Safety of the exercise training programs

To verify the safety of using this kind of aerobic exercise training, a daily record was made of any incidents or adverse effects that could limit the planned exercise.

Statistical analysis

Quantitative variables were described using means and standard deviations. The normality of

the data distribution was determined using the Kolmogorov-Smirnov test. To evaluate the effect of each exercise protocol on the quantitative variables, pre- and post-program values were compared using the Student dependent samples *t*-test. The effect was measured in absolute terms via the difference between the post-program values and those obtained before training. These changes were described with the mean and standard deviation. Comparisons between the two training programs were made using the Student *t* test in the case of quantitative variables and using the χ^2 test of association or Fisher exact test for qualitative variables. All comparisons were made using two-tailed tests, and the level of significance was set at $p < 0.05$. All statistical tests were performed using commercially available software (SPSS, Version 22.0, Inc., Chicago, IL, USA).

Results

A total of 110 patients were included and studied (53 patients in MCT-group and 57 patients in HIIT-group). At the start of the study, there were no significant differences between the groups with regard to clinical characteristics or medication use (as shown in Table 1).

Training data

The intensity of exercise in the MCT-group in the first month was 62.9% ± 7.6% of the VO_2peak reached during the initial CPET (corresponding to the VT_1) and 69.8% ± 8.8% in the second month (corresponding to VT_1 + 10%). The exercise workload applied at the peak intervals in the HIIT--group using the Meyer et al. [12] methodology was 108.3% ± 20.7% (first month) and 126.1% ± 27.8% (second month) of the maximum load reached in the initial CPET, corresponding to 50% of the SRT in the first and second month. The resulting HR during first and second month in HIIT-group was between VT_1 and VT_2.

Cardiopulmonary exercise test

The exercise effort test results for both groups can be seen in Table 3. After 8 weeks of training both exercise programs significantly increased their VO_2peak, the peak exercise workload achieved and the total time of the exercise effort test with a greater increase in the HIIT-group ($p < 0.05$).

The VO_2 at VT_1 and VT_2 significantly increased in both groups, with a significantly higher increase in the HIIT-group ($p < 0.05$). The power at VT_1 significantly increased in both groups, with a greater increase in the HIIT-group ($p < 0.01$), but the power at VT_2 only significantly increased in HIIT-group ($p < 0.001$).

Energy expenditure and mechanical efficiency values

Energy expenditure determined at VT_1, VT_2 and at VO_2peak (Table 3) increased significantly post-training compared to baseline values in both groups but with a significantly higher increase in the HIIT-group.

Mechanical efficiency measured at VT_1, VT_2, and at VO_2peak is reported in Table 3. At VT_1, ME significantly increased in both groups, with a greater increase in the HIIT-group ($p < 0.01$). The ME at VO_2peak and VT_2 only significantly increased in the HIIT-group ($p < 0.001$).

Safety of the training intervention

No incidents or adverse events were recorded that limited the ability of patients to perform the prescribed exercise in either training program.

Discussion

According to available research, this study is the first to examine ME changes in response to 8 weeks of HIIT in patients with CAD. The most relevant finding of the present research was a greater increase in ME of the HIIT-group over MCT-group in intensities related to VT_1, and a significant increase in the ME at VO_2peak and VT_2 in the HIIT-group alone.

Exercise carried out at an intensity greater than VT_2 necessitated an increase of energy contribution of the glycolytic pathway, even when oxidative energetic provision is predominant. Glycolytic activation disturbs the internal cell environment of the muscles involved in the exercise. This means that the mechanism of the excitement-contraction is negatively affected, progressively contributing to the onset of muscular fatigue. This process is related to the muscular capacity to work, and therefore negatively affects mechanical efficiency.

HIIT is a training system that has as its main objective the improvement of VO_2peak, but due to the relative high intensity which is applied (> VT_2), it is also the cause of improvements related to glycolytic metabolism in type II muscular fibres. This provides an improvement in energetic efficiency, in the development of strength and in resistance to fatigue, meaning an improvement in ME.

A relatively high cost of ATPs for muscular contraction is the main cause of the low ME ob-

Table 3. Cardiopulmonary exercise stress test variables in moderate continuous training (MCT) group versus high intensity interval training (HIIT) group at maximal intensity, VT_1 and VT_2.

	MCT group			HIIT group		
	Pretraining	Posttraining	Change	Pretraining	Posttraining	Change
Total exercise time [min]	8.32 ± 1.73	9.67 ± 2.10***	1.35 ± 1.03	8.29 ± 1.69	10.23 ± 2.34***	1.93 ± 1.24‡
VO_2peak [mL/kg/min]	19.50 ± 5.26	22.47 ± 5.71***	2.96 ± 2.33	18.90 ± 4.63	22.78 ± 5.75***	3.88 ± 2.40†
Maximum HR [bpm]	119.19 ± 16.56	123.58 ± 17.84**	4.39 ± 10.97	118.98 ± 16.55	126.47 ± 16.24***	7.49 ± 10.18
Maximum power [W]	114.52 ± 33.94	132.64 ± 41.24***	18.11 ± 16.11	115.78 ± 37.17	153.07 ± 43.99***	38.86 ± 20.11‡
Maximum RER	1.18 ± 0.08	1.19 ± 0.08	0.01 ± 0.09	1.16 ± 0.08	1.16 ± 0.07	0.01 ± 0.08
EE [W]	420.81 ± 153.41	501.15 ± 165.91***	80.34 ± 63.94	423.78 ± 148.93	534.82 ± 190.53***	111.03 ± 77.69†
ME [%]	25.61 ± 4.98	24.91 ± 4.09	–0.70 ± 4.14	24.84 ± 5.99	26.98 ± 5.41***	2.14 ± 3.97‡
VO_2 at VT_1 [mL/kg/min]	10.97 ± 2.74	12.05 ± 2.85***	1.08 ± 1.64	10.40 ± 1.97	12.34 ± 2.45***	1.94 ± 1.42†
HR at VT_1 [bpm]	86.13 ± 10.38	85.26 ± 10.80	–0.86 ± 5.68	87.09 ± 10.30	89.49 ± 11.20***	2.40 ± 6.42†
Power at VT_1 [W]	49.18 ± 18.57	59.94 ± 21.23***	10.76 ± 11.55	49.73 ± 18.32	73.64 ± 19.30***	23.91 ± 10.63‡
RER at VT_1	0.87 ± 0.06	0.86 ± 0.06	0.01 ± 0.05	0.88 ± 0.06	0.85 ± 0.06*	0.02 ± 0.07
EE [W] at VT_1	166.96 ± 74.74	192.41 ± 77.15***	25.45 ± 42.64	155.44 ± 59.27	207.02 ± 70.45***	51.58 ± 45.79‡
ME [%] at VT_1	24.57 ± 5.94	26.78 ± 7.15*	2.20 ± 6.25	24.61 ± 7.93	30.14 ± 8.27***	5.52 ± 5.53‡
VO_2 at VT_2 [mL/kg/min]	15.39 ± 4.12	17.09 ± 4.34***	1.69 ± 2.01	14.64 ± 3.76	17.13 ± 4.19***	2.49 ± 1.94†
HR at VT_2 [bpm]	103.11 ± 15.30	103.92 ± 16.00	0.81 ± 7.30	101.81 ± 13.21	106.11 ± 14.24**	4.29 ± 8.25†
Power at VT_2 [W]	87.34 ± 30.79	99.49 ± 33.36	12.15 ± 14.53	86.26 ± 30.34	114.08 ± 32.18***	27.82 ± 13.30‡
RER at VT_2	1.03 ± 0.06	1.02 ± 0.08	–0.01 ± 0.07	1.02 ± 0.07	1.00 ± 0.06*	–0.02 ± 0.07
EE [W] at VT_2	294.74 ± 116.70	338.35 ± 124.08***	43.61 ± 57.51	285.37 ± 114.51	353.76 ± 132.99***	68.38 ± 61.30†
ME [%] at VT_2	26.76 ± 5.97	27.01 ± 5.17	0.25 ± 4.94	26.32 ± 7.09	29.55 ± 7.12***	3.23 ± 4.95‡

*Within-group difference < 0.05; **Within-group difference < 0.01; ***Within-group difference < 0.001; †Between-group difference < 0.05; ‡Between-group difference < 0.01; HR — heart rate; W — watios, RER — respiratory exchange ratio; VT_1 — ventilatory threshold 1; VT_2 — ventilatory threshold 2; EE — energy expenditure; ME — mechanical efficiency; VT — ventilatory threshold

served in many patients with a cardiovascular pathology [1]. In this context, the improvement in ME (a lower cost of ATPs for the same muscular effort applied) is essentially determined by the improvement of ATP consumption from myosin-ATPase and noncontractile processes related to ion transport associated with the contraction-relaxation cycle (mainly calcium ATPase and to a lesser extent due to Na-K-ATPase). Therefore, any improvement of one of these processes would explain the fall in energy cost of contraction at any exercise intensity level (e.g. VT_1, VT_2, VO_2peak) [1].

The energy required to sustain a given bicycle workload has been previously shown to be correlated with body mass [15, 16]. In the present study, bodyweight decreases in the same proportion in the two training groups during the intervention period, which rules out body mass as an influential factor in the observed modification of ME in the HIIT-group.

A lower O_2 for the same production of power during the bicycle workload could be the result of: 1) A lower ATP cost of the muscular contraction for the same production of effort (an improvement in muscle contraction efficiency); and/or 2) A lower VO_2 for the same level of ATP oxidative resynthesis (an improvement in mitochondrial efficiency). HIIT was able to increase VO_2peak, maximum load (Wmax) and ME to a greater extent, especially by improving the internal cell environment of the muscles active during exercise. However, some authors are of the opinion that the typical short-term adaptations to endurance training such as increased oxygen delivery [17], muscle capillarization and mitochondrial content [18], among others, have a limited impact on ME, meaning that improvements in muscle motor function cannot be excluded as a key element in the improvement of ME.

Moreover, type II muscle fibres have been demonstrated to be substantially less efficient than type I fibres during cycling, as reflected by higher VO_2 in performing exercise at a given power output [19]. Training in aerobic resistance, such as the one employed in the two groups of this study, especially reinforces the oxidative capacity of type I fibres, being able to sustain greater exercise intensity (greater levels of applied resistance). This fact would result in a greater ME.

In athletes HIIT improvement in "metabolic stability" (e.g. reduced changes in concentrations of muscle metabolites such as ADP, AMP, inosine-monophosphate, creatine, inorganic phosphate, and H^+ for a given ATP turnover) may be crucial to limit muscle fatigue, VO_2 slow component, and ME impairment occurring at heavy and severe exercise intensities, particularly through a decrease in the ATP use/power output ratio [20]. Although HIIT in coronary patients are of a less demanding nature from a metabolic point of view, the attainment of partial biochemical muscular adaptations which contribute to the improvement in "metabolic stability" may be speculated upon, and with it ME.

Mechanical inefficiency is mainly related to inactivity and it seems that the exercise intolerance promoted by the disease makes the patients less physically active, with a detraining effect on their peripheral muscles [21]. Lower ME indicates that more energy is consumed at a given work output. Therefore, individuals with lower ME values should be less efficient with respect to performance and may therefore be limited in terms of physical activity [2]. Consequently, an improvement in ME in patients with central limitation (cardiac), will contribute to an improvement in exercise capacity.

Different studies have shown greatest VO_2peak improvements in HIIT respect to continuous load training [7, 8, 22]. In the present research, both exercise programs significantly increased their VO_2peak, with a greater increase in the HIIT-group (difference between group: $p < 0.05$).

In line with the increase of VO_2peak, the maximum load reached increased significantly more in the HIIT-group ($p < 0.001$), reflecting an improvement in the base-acid balance with peak loads.

The two groups of this study improved VO_2 and the load (W) associated with VT_1 and VT_2, with greater improvements in HIIT. Similar results were found in other research studies [23, 24], however other authors have not observed differences associated to the modality of training [7, 8, 25, 26]. While in research conducted by Moholdt and Rognmo the different protocols used may justify the lack of concordance in the results, in previous studies [7, 8], in which a trend for a greater improvement was found in VO_2 and W associated with VT_1, the greater number of patients included in the study meant that the trend had a statistical significance. Physiological variables associated with VT_2 were observed — not an usual occurrence in clinical trials with cardiac patients. HIIT constitutes a training method with a clear objective of improvement inoxidative or aerobic status, but on attaining intensities greater than VT_2, it significantly improves the glycolytic and lactate clearance processes.

Focus on HR related to VT_1 and VT_2, this factor only increased in the HIIT-group, reflecting peripheral metabolic adaptations that allow for sustaining a greater workload. The same results were observed previously [8] suggesting that the

HR associated with ventilatory thresholds are perhaps not a valid variable reflecting an adaptation to exercise.

Additionally, HIIT seems to be a safe exercise modality and did not differ in frequency or magnitude of cardiovascular adverse events during exercise training as compared with MCT, as was shown previously [7].

Conclusions

The results of the present research show that the application of HIIT to patients with chronic ischemic heart disease of low risk resulted in a greater improvement in VO_2peak and in ME at VT_1, than when MCT was applied. Moreover, only the application of HIIT brought about a significant increase in ME at VT_2 and at VO_2peak.

Conflict of interest: None declared

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Two-year prognostic value of mean platelet volume in patients with diabetes and stable coronary artery disease undergoing elective percutaneous coronary intervention

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Abstract

Background: *Mean platelet volume (MPV) is a marker of platelet size and activity, and is associated with a poor prognosis of cardiovascular disease. Studies have shown a relationship between diabetes mellitus (DM) and MPV. This study examined the relationship between admission MPV and 2-year cardiac mortality in patients with DM and stable coronary artery disease (SCAD) undergoing elective percutaneous coronary intervention (PCI).*

Methods: *A total of 1389 patients were enrolled and divided into two groups according to MPV as follows: lower MPV ($n = 908$, MPV ≤ 10.9 fL) and higher MPV ($n = 481$, MPV > 10.9 fL).*

Results: *Body mass index, platelet distribution width, MPV/platelet and glycated hemoglobin (HbA1c) levels were significantly higher in the higher MPV group compared with the lower MPV group (all $p < 0.05$). The platelet count was significantly lower in the higher MPV group compared with the lower MPV group ($p < 0.05$). MPV was positively associated with HbA1c and fasting plasma glucose levels ($r = 0.073$ and 0.061, $p = 0.007$ and 0.023, respectively) in bivariate correlation analysis. The 2-year cardiac mortality rate was 0.7%, and was significantly lower in the lower MPV group than in the higher MPV group in Kaplan-Meier analysis ($p = 0.019$). Receiver operating characteristic analysis showed a good diagnostic value for MPV at predicting long-term cardiac mortality (area under the curve: 0.735, 95% confidence interval [CI]: 0.590–0.880, $p = 0.01$). Elevated MPV was a significant risk factor for 2-year cardiac mortality (hazard ratio: 2.091, 95% CI: 1.075–4.070, $p = 0.030$) in multivariable Cox regression analysis.*

Conclusions: *Mean platelet volume is a strong, independent prognostic factor in PCI-treated patients with DM and SCAD.* (Cardiol J 2019; 26, 2: 138–146)

Key words: diabetes mellitus, stable coronary artery disease, cardiac mortality, percutaneous coronary intervention

Introduction

Platelets play an important role in the onset of cardiovascular disease [1]. Platelet activation is associated with death, myocardial infarction (MI), and other cardiovascular events [2, 3]. Monitoring the function of platelets may help evaluate the severity of coronary artery disease (CAD) and prognosis.

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However, because testing platelet function is a time-consuming, costly, and technically challenging process, it is not widely used. Larger platelets contain more dense granules, express more adhesion receptors, and have higher thrombotic activity, which can reflect the degree of platelet activation [4, 5]. Therefore, platelet volume has been proposed as an indicator of platelet reactivity. Mean platelet volume (MPV) is a precise measure of platelet size, and is reported during a complete blood count analysis. This index is cost-effective and accessible.

Previous studies have reported a relationship between MPV and diabetes mellitus (DM). Platelets of patients with DM are characterized by dysregulation of several signaling pathways, resulting in increased platelet reactivity [6]. Increased platelet size and activity may play a role in the observed higher risk for developing ST-segment elevation myocardial infarction (STEMI) and worse outcomes in patients with DM [7].

Previous studies have examined MPV in the development of CAD [3, 8–10]. MPV is an important factor for helping predict the prognosis of patients with CAD [6, 11–13]. Few studies have examined MPV in patients with stable CAD (SCAD) and DM. Additionally, the prognostic relevance of DM on clinical outcome is less apparent in Asian populations compared with Western populations [14, 15].

The current study aimed to examine the relationship between MPV at admission and clinical outcomes in patients with DM and SCAD undergoing elective percutaneous coronary intervention (PCI). This study also aimed to evaluate whether this index can be used as a marker of long-term prognosis.

Methods

Study population

Patients enrolled were admitted to Fuwai Hospital were diagnosed with SCAD, and underwent elective PCI between January 2013 and December 2013. The study was conducted in accordance with the principles contained within the Declaration of Helsinki, and the Institutional Review Board of Fuwai Hospital approved the study protocol. All participants provided written informed consent before the intervention.

Laboratory examination and procedural details

Venous blood samples were collected at admission in standardized dipotassium EDTA tubes. Samples were tested within 2 h of collection to minimize variations due to sample aging. MPV and platelets were measured using an automated blood counter (Sysmex XN-2000 Hematology System; Sysmex Corp., Kobe, Japan). Before the procedure, if patients with elective PCI were not taking long-term acetylsalicylic acid and clopidogrel, they received a loading dose of clopidogrel (300 mg). Coronary angiography and PCI were performed using standard protocols and guidelines.

Definitions and endpoints

Patients were divided into three groups according to the MPV value (≤ 10.1 fL, group 1; 10.1–10.9 fL, group 2; > 10.9 fL, group 3). Groups 1 and 2 were combined and defined as the lower MPV group (≤ 10.9 fL) and group 3 was defined as the higher MPV group (> 10.9 fL). DM was defined as follows: (a) Pre-existing condition diagnosed before admission (patients on insulin, oral glucose-lowering drugs, or therapeutic diet); and (b) Newly diagnosed DM based on fasting plasma glucose (FPG) levels ≥ 7.0 mmol/L or 2-h plasma glucose levels ≥ 11.1 mmol/L during an oral glucose tolerance test [16]. SCAD was generally characterized by episodes of reversible myocardial demand/supply mismatch related to ischemia or hypoxia usually induced by exercise, emotion, or other stresses, but it may have also spontaneously occurred. Such episodes of ischemia/hypoxia were commonly associated with transient chest discomfort (angina pectoris). SCAD also included stabilized, often asymptomatic, phases that follow acute coronary syndrome (ACS) [17]. Death that could not be attributed to a noncardiac etiology was considered as cardiac mortality, such as intra-stent thrombosis, MI, and sudden death in this cohort.

Follow-up of patients

All patients were scheduled for a 2-year clinical follow-up. Patients were clinically monitored for major cardiovascular events. The primary endpoint was cardiac mortality. Follow-up data were obtained at 30 days, 6 months, 1 year, and 2 years by telephone calls, out-patient follow-ups, or letters. Patients were advised to return for coronary angiography if clinically indicated by symptoms or documentation of myocardial ischemia.

Statistical analysis

Continuous variables are presented as mean ± standard deviation (SD) or median (interquartile range) and were compared using the Student t-test or Mann-Whitney U test, as appropriate. The Shapiro-Wilk test was used to determine whether ran-

dom samples had a normal distribution. Categorical variables are presented as numbers and percentages, and were compared using the χ^2 test or the Fisher exact test. In-hospital and 2-year survival was evaluated using the Kaplan-Meier method and compared using the log-rank test. Relationships between MPV and variables were estimated using the Spearman rank correlation coefficient. Receiver operating characteristic (ROC) curves were estimated for MPV. ROC analysis was used to identify possible cut-offs for predicting 2-year cardiac mortality. Clinically important variables (age, sex, body mass index, hypertension, hyperlipidemia, ejection fraction, estimated glomerular filtration rate, high-sensitivity C-reactive protein) were entered into multivariate Cox analysis. Multivariate analysis was performed to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) for identifying independent predictors of 2-year cardiac mortality, while adjusting for potential confounders. A two-tailed p value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS 23.0 (SPSS Inc., College Station, TX).

Results

A total of 1389 consecutive patients were enrolled. Follow-up at 2 years was completed for 1380 (99.4%) patients.

Patient characteristics and outcomes according to MPV level and DM

Baseline characteristics according to MPV and DM are shown in Table 1. The higher MPV group had a higher body mass index ($p = 0.003$), platelet distribution width ($p < 0.001$), MPV/PLT ($p < 0.001$), and glycated hemoglobin (HbA1c) levels ($p = 0.023$), but a lower platelet count ($p < 0.001$), compared with the lower MPV group. Angiographic characteristics according to MPV are shown in Table 2. The higher MPV group had a higher SYNTAX score and more often had severe CAD (left main stenosis and/or 3-vessel disease) compared with the lower MPV group, but these differences were not significant. There were no significant differences in lesions of the left anterior descending, left circumflex coronary, and right coronary arteries between the groups.

Effect of high MPV on cardiac mortality of patients with DM

Over the 2-year follow-up, 3 of 908 patients died in the lower MPV group and 7 of 481 patients died in the higher MPV group for cardiac reasons ($p = 0.038$) (Table 3). Among all patients, 7 died of stent thrombosis, 1 died of MI, and 2 died of sudden cardiac death. The cardiac mortality rate was 0.7%. Kaplan-Meier survival analysis showed a higher 2-year cardiac mortality rate in the higher MPV group than in the lower MPV group ($p = 0.019$) (Fig. 1). Cox regression showed that MPV was significantly associated with 2-year cardiac mortality when analyzed as a continuous variable in the univariate model (HR = 2.090, 95% CI: 1.217–3.589, $p = 0.008$) and multivariate models. Similar findings were observed when MPV was analyzed as a binary variable (Table 4).

Patients with DM with or without requirement for insulin

Mean platelet volume was similar in patients with DM who required insulin and those who did not require insulin ($p = 0.853$). No significant difference in cardiac mortality was observed between patients with or without insulin ($p = 0.986$). Cox regression analysis showed no significant difference between patients with or without insulin (HR = 0.892, 95% CI: 0.230–3.463, $p = 0.869$).

ROC analysis

In patients with DM, ROC analysis showed good diagnostic value for MPV at predicting 2-year cardiac mortality (area under the curve = 0.735, 95% CI: 0.590–0.880, $p = 0.01$) (Fig. 2). The cut-off value was 10.65 fL.

Bivariate analysis of MPV, HbA1c, and FPG

Mean platelet volume was significantly positively correlated with HbA1c ($r = 0.073$, $p = 0.007$) and FPG levels ($r = 0.061$, $p = 0.023$) in bivariate analysis (Fig. 3).

Discussion

In this study, the relationship between MPV at admission and 2-year cardiac mortality in patients with DM and SCAD who underwent elective PCI was examined. The present study found that: 1) The cardiac mortality rate was significantly higher in the higher MPV group compared with the lower MPV group, 2) MPV was positively correlated with HbA1c and FPG levels, although the association was weak, and 3) MPV was not associated with the extent of CAD.

Mean platelet volume is influenced by multiple risk factors for CAD, including DM, impaired fasting glucose, hyperlipidemia, and metabolic

Table 1. Basic characteristics of the study population.

	MPV ≤ 10.9 (n = 908)	MPV > 10.9 (n = 481)	P
Age [years]	59.2 ± 9.5	58.7 ± 9.4	0.409
Sex (male)	691 (76.1%)	367 (76.3%)	0.934
Weight [kg]	74.2 ± 11.3	76.2 ± 11.6	0.002
BMI [kg/m^2]	26.1 ± 3.1	26.7 ± 3.3	0.003
Systolic BP [mmHg]	129.2 ± 16.6	129.9 ± 17.2	0.475
LVEF [%]	63.4 ± 7.5	63.0 ± 6.9	0.329
Past medical history:			
Dyslipidemia	698 (76.9%)	340 (70.7%)	0.012
Smoker:			0.615
Active smoker	482 (53.1%)	267 (55.5%)	
Previous smoker	15 (1.7%)	6 (1.2%)	
Hypertension	621 (68.4%)	337 (70.1%)	0.522
Previous MI	227 (25.0%)	141 (29.3%)	0.083
Previous PCI	290 (31.9%)	135 (28.1%)	0.136
Previous CABG	40 (4.4%)	32 (6.7%)	0.072
Previous CVD	114 (12.6%)	59 (12.3%)	0.877
Laboratory finding:			
Platelet count [×10^9/L]	206.7 ± 50.6	173.5 ± 45.4	< 0.001
MPV/PLT	0.05 ± 0.01	0.07 ± 0.02	< 0.001
Hemoglobin [g/L]	142.1 ± 16.1	143.8 ± 14.5	0.049
Hematocrit [%]	41.4 ± 4.2	42.1 ± 3.9	0.004
WBC [×10^9/L]	6.72 ± 1.71	6.72 ± 1.77	0.949
RBC [×10^{12}/L]	4.64 ± 0.52	4.69 ± 0.50	0.059
RDW [%]	12.8 ± 0.6	12.8 ± 0.7	0.177
PDW [%]	11.5 ± 1.0	14.8 ± 1.6	< 0.001
FPG [mmol/L]	7.4 ± 2.3	7.6 ± 2.5	0.061
eGFR [mL/min/1.73 m^2]	91.9 ± 14.5	91.2 ± 15.8	0.379
HbA1c [%]	7.7 ± 1.3	7.8 ± 1.4	0.023
hsCRP [mg/L]	1.47 (0.77, 3.07)	1.44 (0.73, 3.17)	0.539
BNP [pmol/L]	444 (568, 748)	591 (447, 791)	0.262
ET-1 [pmol/L]	0.29 ± 0.17	0.30 ± 0.15	0.396
Uric acid [mg/dL]	5.52 ± 1.34	5.64 ± 1.45	0.128
TG [mmol/L]	1.47 (1.12, 2.05)	1.56 (1.12, 2.23)	0.076
TC [mmol/L]	3.86 (3.30, 4.64)	3.90 (3.35, 4.72)	0.556
HDL-C [mmol/L]	0.99 (0.84, 1.14)	0.97 (0.81, 1.14)	0.120
LDL-C [mmol/L]	2.20 (1.77, 2.83)	2.24 (1.78, 2.81)	0.876
Concomitant medication in hospital:			
Acetylsalicylic acid	901 (99.2%)	475 (98.8%)	0.380
Clopidogrel	896 (98.7%)	476 (99.0%)	0.649
Beta-blocker	849 (93.5%)	439 (91.3%)	0.127
Statins	860 (94.7%)	459 (95.4%)	0.564

Data are presented as number (percentage) for categorical data and mean ± standard deviation) or median (interquartile range) for continuous data, depending on distribution of the data. Hypertension was defined as systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihypertensive medication. Dyslipidemia was defined as total cholesterol levels > 5.98 mmol/L, low-density lipoprotein levels ≥ 2.59 mmol/L, or high-density lipoprotein levels ≤ 1.59 mmol/L. The estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration Study equation.
BMI — body mass index; BNP — B-type natriuretic peptide; BP — blood pressure; CABG — coronary artery bypass grafting; CVD — cardiovascular disease; eGFR — estimated glomerular filtration rate; ET-1 — endothelin-1; FPG — fasting plasma glucose; HbAlc — glycated hemoglobin; HDL-C — high-density lipoprotein cholesterol; hs-CRP — high-sensitivity C-reactive protein; LDL-C — low-density lipoprotein cholesterol; LVEF — left ventricular ejection fraction; MI — myocardial infarction; MPV — mean platelet volume; PCI — percutaneous coronary intervention; PDW — platelet distribution width; RBC — red blood cells; RDW — red cell distribution width; TC — totalcholesterol; TG — triglycerides; WBC — white blood cells

Table 2. Angiographic and procedural characteristics.

	MPV ≤ 10.9 (n = 908)	MPV > 10.9 (n = 481)	P
Angiographic features:			
Multivessel disease	743 (71.8%)	410 (85.2%)	0.266
LM/trivessel disease	483 (53.2%)	272 (56.5%)	0.232
Artery treated:			
LM	21 (2.3%)	16 (3.3%)	0.264
LAD	811 (89.3%)	420 (87.3%)	0.264
LCX	171 (18.8%)	86 (17.9%)	0.663
RCA	168 (18.5%)	117 (24.3%)	0.011
Complex type C lesions	528 (58.1%)	284 (59.0%)	0.865
Lesion length [mm]	32.4 ± 18.6	33.2 ± 17.0	0.445
Vessel diameter [mm]	3.10 ± 0.51	3.11 ± 0.52	0.564
Calcified lesions	540 (59.5%)	269 (55.9%)	0.161
Bifurcation	132 (14.5%)	85 (17.7%)	0.126
Intracoronary thrombus	40 (4.5%)	16 (3.4%)	0.242
Chronic occlusion	179 (19.7%)	92 (19.1%)	0.793
In-stent restenosis	42 (4.6%)	24 (5.0%)	0.525
PMI	12 (1.3%)	3 (0.6%)	0.231
SYNTAX score	13.0 ± 8.3	13.2 ± 7.7	0.541
TIMI flow:			0.807
3	872 (96.0%)	462 (96.0%)	
2	11 (1.2%)	6 (1.2%)	
1	5 (0.6%)	1 (0.2%)	
0	20 (2.2%)	12 (2.5%)	
Successful PCI	856 (94.3%)	464 (96.5%)	0.181
Stent implantation	844 (93.0%)	457 (95.0%)	0.134

Data are presented as number (percentage) for categorical data and mean ± standard deviation for continuous data. LAD — left anterior descending artery; LCX — left circumflex coronary artery; LM — left main; MPV — mean platelet volume; RCA — right coronary artery; PMI — periprocedural myocardial infarction; TIMI — Thrombolysis in Myocardial Infarction

Table 3. Two-year follow-up clinical outcomes.

	MPV ≤ 10.9 (n = 908)	MPV > 10.9 (n = 481)	P
All-cause death	10 (1.1%)	9 (1.9%)	0.237
Cardiac mortality	3 (0.3%)	7 (1.5%)	0.038
Myocardial infarction	21 (2.3%)	5 (1.0%)	0.143
Revascularization	82 (9.0%)	47 (9.8%)	0.651
TVR	55 (6.1%)	30 (6.2%)	0.894
TLR	46 (5.1%)	22 (4.6%)	0.686
Stent thrombosis	10 (1.1%)	4 (0.8%)	0.782
Stroke	15 (1.7%)	7 (1.5%)	0.780
Bleeding	59 (6.5%)	32 (6.7%)	0.912
Severe bleeding	4 (0.4%)	0 (0.0%)	0.305
MACE	116 (12.8%)	65 (13.5%)	0.697

Data are presented as number (percentage). MACE — major adverse cardiovascular events; MPV — mean platelet volume; TLR — target lesion revascularization; TVR — target vessel revascularization

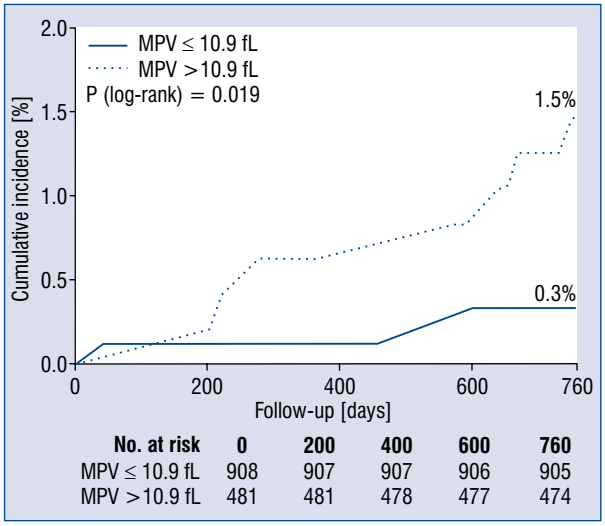

Figure 1. Kaplan–Meier curves for cardiac mortality. Cumulative Kaplan-Meier event curves for 2-year cardiac mortality were significantly higher in the higher mean platelet volume (MPV) group than in the lower MPV group.

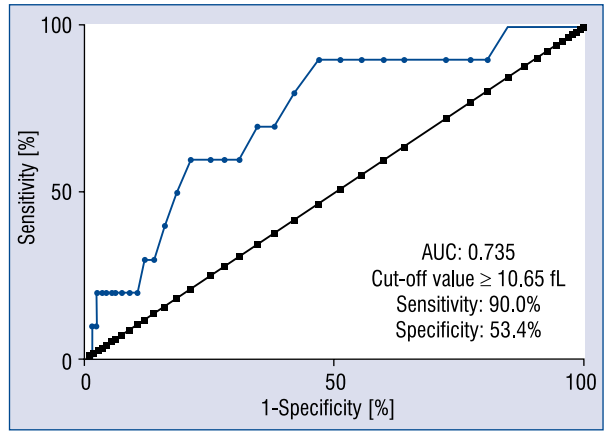

Figure 2. Receiver operating characteristic curve of mean platelet volume for predicting 2-year cardiac mortality; AUC — area under the curve.

syndrome [18–20]. In a study of 1411 patients [10], MPV was found to correlate with the frequency of DM and baseline glycemia. Shimodaira et al. [21] found that in prediabetic and normoglycemic patients, MPV was positively correlated with FPG levels. Verdoia et al. [22] also observed a similar phenomenon in their study of 3414 patients who underwent coronary angiography. In this study, it was found that MPV was positively correlated with HbA1c and FPG levels, but this association was weak. A possible reason for this finding may be that some other features, such as hypertension and other metabolic disorders, in addition to diabetes, affected platelet size.

Previous studies on the relationship between MPV and the severity of CAD in patients with DM are inconsistent. Sahin et al. [23] found that increased MPV was positively associated with the severity of CAD in patients with STEMI and DM. Abali et al. [24] reported that a high MPV may be an effective marker in determining the severity of CAD in patients with DM, and that a high MPV level may be associated with CAD pathophysiology in patients with DM. However, Lekston et al. [6] did not find a relationship between MPV and the number of diseased coronary arteries in patients with STEMI and DM who received primary PCI. In the current study, MPV in patients with DM who received elective PCI was examined. It was found that the incidence rate of left main and/or 3-vessel disease and SYNTAX score appeared to be higher in the

Table 4. Association between mean platelet volume and cardiac mortality.

	HR	95% CI	P
MPV (per 1 fL increment)	2.090	1.217–3.589	0.008
Model 1	2.063	1.218–3.494	0.007
Model 2	2.016	1.051–3.870	0.035
Model 3	2.091	1.075–4.070	0.030
MPV (2 groups)	4.401	1.138–17.017	0.032
Model 1	4.577	1.181–17.737	0.028
Model 2	5.652	1.270–25.146	0.023
Model 3	5.773	1.283–25.981	0.022

Model 1: Adjusted for age, sex, and body mass index.
Model 2: Model 1 + hypertension, hyperlipidemia, and left ventricular ejection fraction.
Model 3: Model 2 + estimated glomerular filtration rate and high-sensitivity C-reactive protein.
CI — confidence interval; HR — hazard ratio

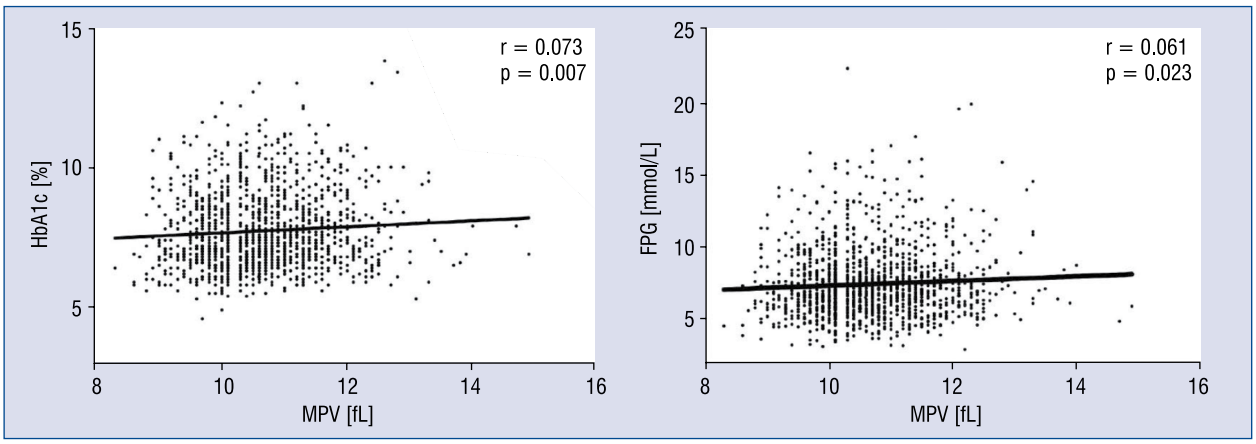

Figure 3. Correlation analysis. Mean platelet volume (MPV) was positively correlated with glycated hemoglobin (HbA1c) levels (**A**) and MPV was positively correlated with fasting plasma glucose (FPG) levels (**B**).

higher MPV group, but this was not significant. Further studies are required to determine the relationship between MPV and the severity of CAD in patients with DM.

Previous studies have reported that pre-procedural elevated MPV is associated with the incidence of major adverse cardiac events following PCI [25]. Most of these studies were conducted in patients with ACS. A meta-analysis [26] reported that MPV was higher in patients who developed cardiovascular events than in non-cardiovascular event patients, particularly those with MI and death. MPV may be a predictive factor of future MI or death in patients with ACS. Lekston et al. [6] studied the association between MPV at admission and clinical outcomes in patients with DM and STEMI. They found that MPV had good prognostic value for in-hospital and late mortality. In the current study, it was found that MPV had good prognostic value for 2-year cardiac mortality in patients with DM and SCAD, which is consistent with previous studies. However, Shah et al. [27] analyzed MPV in 1512 patients who received PCI and did not find any correlation between MPV and long-term mortality. A possible reason for this lack of findings is that they enrolled diabetic and non-diabetic patients.

The possible mechanisms behind increased major cardiovascular events in patients with high MPV may be an increase in platelet activity and aggregation. Platelet turnover also increases in these patients. There is an increased release of young, large, and reactive platelets from megakaryocytes in bone marrow, which results in an increased measurement of MPV. High platelet turnover has been reported to be associated with soluble P-selectin (a platelet activation marker), platelet aggregation [28], and inadequate responses to antiplatelet drugs [29, 30]. Platelets in people with type 2 DM adhere to the vascular endothelium and aggregate more readily than those in healthy people. Loss of sensitivity to the normal restraints exercised by prostacyclin and nitric oxide generated by the vascular endothelium is a major defect in platelet function. Insulin is a natural antagonist of platelet hyperactivity. Insulin sensitizes platelets to PGI2 and enhances endothelial generation of PGI2 and nitric oxide. Defects in the action of insulin in DM create a condition of disordered platelet activity, which is conducive to macrovascular and microvascular events [31].

Limitations of the study

This study has some limitations. First, this was an observational, single-center study and was thus prone to bias and unintentional confounding. Second, we did not assess platelet function at the same time. Finally, the cohort only included those who underwent elective PCI rather than PCI following ACS. Therefore, the rate of major cardiovascular events was lower compared with similar previous studies.

Conclusions

Mean platelet volume is a strong, independent prognostic factor in PCI-treated patients with DM and SCAD.

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Conflict of interest: None declared

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Effect of coenzyme Q_{10} in Europeans with chronic heart failure: A sub-group analysis of the Q-SYMBIO randomized double-blind trial

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Abstract

Background: *Geographical differences in patient characteristics, management and outcomes in heart failure (HF) trials are well recognized. The aim of this study was to assess the consistency of the treatment effect of coenzyme Q_{10} (CoQ_{10}) in the European sub-population of Q-SYMBIO, a randomized double-blind multinational trial of treatment with CoQ_{10}, in addition to standard therapy in chronic HF.*

Methods: *Patients with moderate to severe HF were randomized to CoQ_{10} 300 mg daily or placebo in addition to standard therapy. At 3 months the primary short-term endpoints were changes in New York Heart Association (NYHA) functional classification, 6-min walk test, and levels of N-terminal pro–B type natriuretic peptide. At 2 years the primary long-term endpoint was major adverse cardiovascular events (MACE).*

Results: *There were no significant changes in short-term endpoints. The primary long-term endpoint of MACE was reached by significantly fewer patients in the CoQ_{10} group (n = 10, 9%) compared to the placebo group (n = 33, 27%, p = 0.001). The following secondary endpoints were significantly improved in the CoQ_{10} group compared with the placebo group: all-cause and cardiovascular mortality, NYHA classification and ejection fraction. In the European sub-population, when compared to the whole group, there was greater adherence to guideline directed therapy and similar results for short- and long-term endpoints. A new finding revealed a significant improvement in left ventricular ejection fraction.*

Conclusions: *The therapeutic efficacy of CoQ_{10} demonstrated in the Q-SYMBIO study was confirmed in the European sub-population in terms of safely reducing MACE, all-cause mortality, cardiovascular mortality, hospitalization and improvement of symptoms.* (Cardiol J 2019; 26, 2: 147–156)

Key words: chronic heart failure, coenzyme CoQ_{10}, ubiquinone, randomized controlled trial, major adverse cardiovascular events, mortality, hospitalization

Introduction

Heart failure (HF) is a progressive worsening of cardiac function, due to a variety of causes including ischemic heart disease, hypertension, cardiomyopathy and diabetes. Despite considerable advances in treatment options, HF continues to be associated with a high symptomatic burden, frequent hospitalizations and a poor long-term prognosis with 50% of HF patients dying within 5 years of diagnosis [1].

Coenzyme Q_{10} (CoQ_{10}) is an essential component in the production of cellular energy (ATP) in mitochondria. In addition, CoQ_{10} has strong antioxidative properties that protects against cellular damage from free radicals including reactive oxygen species [2–4]. CoQ_{10} is primarily synthesized endogenously and in sufficient amounts during

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normal physiological conditions. However, endogenous production of CoQ_{10} declines with age and an actual deficiency is observed in a number of pathophysiological conditions including HF [5–7]. The biochemical rationale of CoQ_{10} supplementation in HF patients is to correct a documented deficit in heart tissue CoQ_{10} that may lead to failure in mitochondrial bioenergetics and a compromised cellular antioxidant capacity of the myocardium [8–11].

The Q-SYMBIO study, a multinational prospective, randomized, double-blind trial, demonstrated that treatment with CoQ_{10}, in addition to standard therapy for patients with chronic HF, improved symptoms and reduced adverse cardiovascular events and mortality [12]. In Q-SYMBIO, patients with HF were enrolled from European and non-European (mainly Asian) centers.

Geographic differences in patient characteristics and management have the potential to affect the outcome of clinical trials. These differences have recently been analyzed and described in large HF trials [13–15]. For example, the Angiotensin––Neprilysin Inhibition versus Enalapril in Heart Failure (PARADIGM) trial included patients from 5 regions including European and Asian countries, and notable regional differences were found in baseline characteristics and background HF therapy. Furthermore, differences in event-rates of HF outcomes were found, however the benefit of angiotensin–neprilysin inhibition was consistent across regions [16].

The aim of the present study was to assess the consistency of the treatment effect of CoQ_{10} in a European sub-population (n = 231) of the total population of Q-SYMBIO (n = 420).

Methods

The efficacy of CoQ_{10} in a European sub-population (n = 231) of the Q-SYMBIO trial (n = 420) by post-hoc analysis of baseline characteristics for short-term (3 months) and long-term (2 years) endpoints were investigated. Patients with moderate to severe HF were enrolled from 14 centers in 6 European countries (Poland, Denmark, Sweden, Hungary, Austria and Slovakia) and were randomized in parallel groups to either CoQ_{10} 300 mg (Ubiquinone, Pharma Nord ApS) daily (n = 108) or placebo (n = 123) in addition to standard HF therapy.

The short-term primary endpoints were changes in New York Heart Association (NYHA) functional class, 6-min walk test (6MWT), and N-terminal pro–B-type natriuretic peptide (NT-proBNP). The secondary short-term endpoint was the scoring of symptoms (dyspnea, fatigue, and change in symptoms) by patients on visual analogue scale (VAS).

The primary long-term endpoint was a composite of major adverse cardiovascular events (MACE) defined as unplanned hospitalization due to worsening of HF, cardiovascular death, urgent cardiac transplantation or mechanical support using time to first event analysis. Secondary long-term endpoints were mortality, changes in NYHA functional class, NT-proBNP and echocardiography (left ventricular ejection fraction [LVEF] and cavity dimensions).

Samples of serum were shipped to the core Biochemical Laboratory in Ancona, Italy and assayed for levels of CoQ_{10} by using high-performance liquid chromatography with ultraviolet detection [17] and NT-proBNP using the Elecsys 2010 immunoassay method (Roche Diagnostics, Mannheim, Germany) [18].

Statistical analysis

Descriptive analyses of baseline data were reported as frequencies. Percentages for categorical data and for continuous data were reported as mean ± standard deviation or mean ± standard error for normally distributed data and median and lower upper quartile for non-normal data. Baseline characteristics were compared for indepedence between patient group using the Fisher exact test for categorical data and two-tailed t-test for continous data. The significance of treatment on continuous responses was analyzed by a linear model with each investigation center treated as a random intercept effect. The treatment effects were analyzed and adjusted for pre-defined confounders. A χ^2 test for independence with exact p values was calculated using the Fisher exact test for the evaluation of the treatment effect on categorical responses. Cumulative incidence curves for the risk of MACE, hospital stay for HF, total cardiovascular mortality, and all-cause mortality were constructed by the Kaplan-Meier method and were analyzed by the Cox proportional hazards regression model stratified according to the center. The rates for adverse effects were compared between treatment groups by means of a χ^2 test for independence. For the short-term primary endpoints, the pre-specified objective was reached if the difference between the groups in all three endpoints had a p value < 0.05. For the primary long-term endpoint MACE, the pre-specified objective was reached if the difference between the groups had a p value < 0.05. For secondary endpoints, p values < 0.05 were

used to assess statistical significance. All data were analyzed with the statistical analysis program Stata/SE 11.2 for Windows (StataCorp LP, College Station, Texas).

Results

Baseline characteristics

The two treatment groups of the European sub-population were similar regarding baseline characteristics except male gender, CoQ_{10} (83%) vs. placebo (71%) ($p = 0.03$) and systolic blood pressure, CoQ_{10} (127 mmHg) vs. placebo (121 mmHg) ($p = 0.03$; Table 1). At the beginning of the study, an average of 90% of patients were classified as NYHA class III, 6% as NYHA class II and 6% as NYHA class IV and with an LVEF of 33%. The two treatment groups were balanced for medication usage with an average of 92% patients receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, 88% receiving beta-blockers, 32% digoxin, 84% diuretics, 37% anti-coagulants, 55% aldosterone antagonists, 57% statin derivatives and 26% diabetic medication (Table 1).

Changes in serum CoQ_{10} levels

Changes in biochemical status were examined at short term (3 months) and long-term follow-up (2 years). After 3 months, serum CoQ_{10} significantly increased 3-fold in the CoQ_{10} group ($p < 0.001$) from 0.95 ± 0.08 μg/mL (mean ± SE) at baseline to 3.42 ± 0.21 μg/mL and was maintained during the study period with a level of 3.55 ± 0.34 μg/mL ($p < 0.001$) after 2 years. In the placebo group, there was a non-significant decrease in mean serum CoQ_{10} from 0.90 ± 0.07 μg/mL at baseline to 0.76 ± 0.04 μg/mL after 2 years (Table 2).

Effect on short-term endpoints

At 3 months there was a borderline significant reduction in serum NT-proBNP ($p = 0.052$) in the CoQ_{10} group compared to baseline but not in the placebo group (Table 2). There were no changes from baseline in the specified short-term endpoints NYHA functional class, VAS score, 6MWT or heart rate in either treatment group or between groups (Table 3).

Effect on long-term endpoints

The long-term primary endpoint MACE was reached by significantly fewer patients in the CoQ_{10} group (n = 10, 9%) compared to the placebo group (n = 33, 27%, $p = 0.001$; Table 4). A significant risk reduction in MACE with CoQ_{10} compared to placebo was found from a Cox proportional hazards regression analysis stratified by center (hazard ratio [HR] 0.23; 95% confidence interval [CI] 0.11–0.51; $p < 0.001$; Fig. 1).

A significantly greater proportion of patients in the CoQ_{10} group improved by at least one grade in NYHA functional classification after 2 years (n = 39, 48%) compared to the placebo group (n = 19, 25%, $p = 0.003$; Table 3). In the CoQ_{10} group there was a significant improvement of 6% in LVEF compared to baseline ($p = 0.021$) but there was no significant change in the placebo group ($p = 0.234$; Table 3). In the CoQ_{10} group, compared to baseline, serum NT-proBNP was reduced by a mean of 702 pg/mL (28%) in the CoQ_{10} group and a reduction of 276 pg/mL (12%) in the placebo group. Neither of these values were significantly different from baseline nor were there differences between the two groups (Table 2). For heart rate and blood pressure there were no significant changes from baseline with treatment in either group nor were there any between-group differences (Table 3).

All-cause mortality was lower in the CoQ_{10} group, 10 (9%) patients vs. 24 (20%) patients in the placebo group, corresponding to a relative reduction of 53% ($p = 0.040$). Using a Cox proportional hazards regression analysis stratified by center revealed a significant reduction in all-cause mortality with CoQ_{10} compared to placebo (HR 0.37; 95% CI 0.16–0.82; $p = 0.014$; Fig. 2). The total number of cardiovascular deaths, was also lower in the CoQ_{10} group compared to the placebo group, 9 (8%) vs. 21 (17%) corresponding to a relative reduction of 51% ($p = 0.052$). From a Cox regression analysis stratified by center, the HR (CoQ_{10} vs. placebo) was 0.36 (95% CI 0.15–0.85; $p = 0.020$). Three (3%) patients were hospitalized due to worsening HF in the CoQ_{10} group vs. 16 (13%) patients in the placebo group ($p = 0.007$). The risk of unplanned hospitalization due to worsening HF counted as MACE was significantly lower in the CoQ_{10} group with a HR of 0.07 (95% CI 0.01–0.36; $p = 0.001$) using a Cox proportional hazards regression analysis stratified by center.

Adverse effects

There were no differences in the total number of adverse events in the CoQ_{10} group, 17 (16%) vs. 28 (23%) in the placebo group ($p = 0.188$).

Comparison of the European population with the total population

Baseline patient characteristics and management. In comparison with the whole

Table 1. Baseline characteristics of European patients.

Baseline characteristics	Standard HF therapy + CoQ_{10} (47%, n = 108)	Standard HF therapy + placebo (53%, n = 123)
Age [years]	65.7 ± 10	64.0 ± 12
Male gender*	90 (83%)	87 (71%)
Weight [kg]	83.7 ± 18	84.8 ± 18
BMI [kg/m^2]	29 ± 5	29 ± 7
Heart rate [bpm]	72 ± 12	75 ± 12
Systolic BP [mmHg]*	127 ± 21	121 ± 19
Diastolic BP [mmHg]	77 ± 11	74 ± 11
Sinus rhythm	67 (62%)	77 (63%)
Atrial fibrillation	27 (25%)	32 (26%)
Rhythm, other (pace)	14 (13%)	14 (11%)
Ischemic heart disease	68 (63%)	84 (68%)
Dilated cardiomyopathy	35 (32%)	38 (31%)
Valvular heart disease	5 (5%)	1 (1%)
Duration of HF [months]	42 ± 59	39 ± 41
NYHA class II	6 (6%)	7 (6%)
NYHA class III	97 (90%)	109 (89%)
NYHA class IV	5 (5%)	7 (6%)
Left ventricular EF [%], [range]	33 ± 12 [10–65]	33 ± 12 [10–70]
Left ventricular EDD [mm]	64 ± 10	62 ± 11
Left ventricular ESD [mm]	51 ± 12	50 ± 13
6MWT [m], [range]	331 ± 91 [25–525]	321 ± 90 [90–490]
Serum CoQ_{10} [μg/mL]§	0.95 ± 0.08	0.90 ± 0.07
NT-proBNP [pg/mL]§†	2470 ± 369, p50: 1208	2335 ± 398, p50: 1174
Use of medications:		
ACEI/ARBs	99 (92%)	112 (91%)
Beta-blockers	94 (87%)	110 (89%)
Digoxin	35 (32%)	39 (32%)
Diuretics	90 (83%)	104 (85%)
Aldosterone antagonists	59 (55%)	66 (54%)
Statins	62 (57%)	69 (56%)
Anticoagulants	38 (35%)	48 (39%)
Diabetes medication	27 (25%)	32 (26%)
Device therapy:		
Cardiac resynchronization device	2	5
Implanted cardioverter defibrillator	3	4

Values are mean ± standard deviation, number (percentage), mean ± standard deviation [range], mean ± standard deviation (median, p50), or number. §Values are mean ± standard error. †To convert values for NT-proBNP to picomoles per liter, divide by 8.457, *p = 0.03. ACEI/ARB — angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BMI — body mass index; BP — blood pressure CoQ_{10} — coenzyme Q10; EDD — end-diastolic diameter; ESD — end-systolic diameter; EF — ejection fraction; HF — heart failure; NT-proBNP — N-terminal pro–B-type natriuretic peptide; NYHA — New York Heart Association; 6MWT — 6-min walk test

population of Q-SYMBIO, the Europeans were slightly older (mean 65 vs. 62 years), heavier (84.3 vs. 77.5 kg) with a lower heart rate (73 vs. 81 bpm), and a higher prevalence of atrial fibrillation (26% vs 18%) (Table 5). The majority of both populations were classified as NYHA class III (89% and 87%). Almost half as many of the European patients were classified as NYHA IV compared to the total population (5% vs. 9%). The lower percentage of patients with end-stage HF in the European population was in accordance with a greater average performance

Table 2. Biochemical assessments at baseline at 3 months and 2 years.

Variable	CoQ_{10} (mean ± SE) 3 months: n = 80 2 years: n = 40	Placebo (mean ± SE) 3 months: n= 88 2 years: n = 45
Serum CoQ_{10} [μg/mL]:		
Baseline	0.95 ± 0.08	0.90 ± 0.07
3 months	3.42 ± 0.21*	0.82 ± 0.06
2 years	3.55 ± 0.34*	0.76 ± 0.04
Serum NT-proBNP [pg/mL]†		
Baseline	2470 ± 369	2335 ± 398
3 months	2144 ± 370§	2343 ± 418
2 years	1768 ± 375	2059 ± 390

*p < 0.001 vs. baseline, §p = 0.052 vs. baseline, †To convert values for NT-proBNP to picomoles per liter, divide by 8.457. CoQ_{10} — coenzyme Q_{10}; NT-proBNP — N-terminal pro–B-type natriuretic peptide; SE — standard error

Table 3. Clinical and echocardiographic assessment changes from baseline.

Variable	3 months		2 years	
	CoQ_{10} (n = 98)	Placebo (n = 109)	CoQ_{10} (n = 81)	Placebo (n = 77)
NYHA classification:				
Improvement	27 (28%)	26 (24%)	39 (48%)*	19 (25%)
Unchanged	68 (69%)	82 (75%)	42 (52%)	58 (75%)
Deterioration	3 (3%)	1 (1%)	1 (1%)	3 (4%)
VAS score (% ± SE):				
Dyspnea	–9.6 ± 2.4	–6.4 ± 2.3	NR	NR
Fatigue	–8.7 ± 2.6	–8.7 ± 2.1	NR	NR
General symptoms change	–7 ± 8.5	–7 ± 8.6	NR	NR
6MWT [m]	+25 ± 60	+20 ± 71	+19 ± 75	+2 ± 102
Heart rate [bpm]	0 (72 ± 15)	0 (74 ± 14)	0 (72 ± 13)	–1 (73 ± 14)
Systolic BP [mmHg]	0 (127 ± 23)	0 (121 ± 18)	0 (127 ± 21)	–3 (124 ± 20)
Diastolic BP [mmHg]	–3 (74 ± 12)	–1 (75 ± 12)	0 (74 ± 10)	0 (75 ± 11)
Left ventricular EF [%]	+3 (36 ± 13)	+1 (34 ± 12)	+6 (39 ± 12)**	+2 (35 ± 14)
Left ventricular EDD [mm]	–2 (62 ± 10)	0 (62 ± 10)	–1 (61 ± 9)	–1 (61 ± 11)
Left ventricular ESD [mm]	–2 (49 ± 11)	–2 (48 ± 12)	–2 (47 ± 13)	0 (48 ± 15)

Values given are ± standard deviation unless otherwise stated. *p = 0.003, **p = 0.021 for CoQ_{10} vs. placebo at 2 years, BP — blood pressure; CoQ_{10} — coenzyme Q_{10}; EDD — end-diastolic diameter; EF — ejection fraction; ESD — end-systolic diameter; 6MWT — 6-min walk test; NR — not recorded; NYHA — New York Heart Association; SE — standard error; VAS — Visual Analogue Scale

Table 4. Major adverse cardiovascular events at 2 years.

Endpoint	CoQ_{10} (n = 108)	Placebo (n = 123)
Death due to MI	2	3
Death due to HF	1	6
Sudden cardiac death	4	8
Hospitalization due to acute HF and PE	0	1
Hospitalization due to worsening HF	3	15
Total	10 (9%)*	33 (27%)

*p = 0.001. CoQ_{10} — coenzyme Q_{10}; HF — heart failure; MI — myocardial infarction; PE — pulmonary embolism

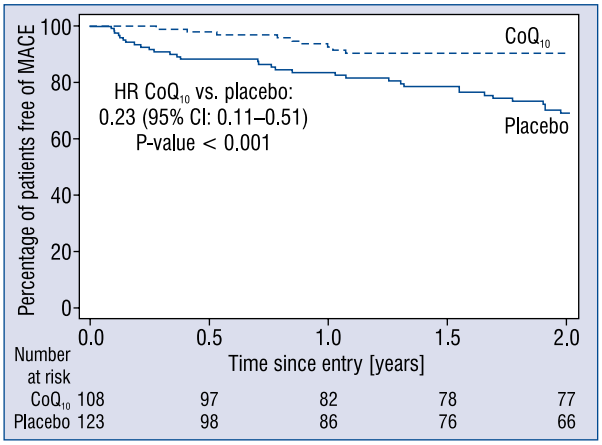

Figure 1. Estimates of the time to primary endpoint of major adverse cardiovascular events (MACE) in the placebo group (solid line) and the coenzyme Q_{10} (CoQ_{10}) group (dashed line). The primary endpoint was composite MACE of hospital stay for worsening heart failure, cardiovascular death, mechanical support, or urgent cardiac transplantation; CI — confidence interval; HR — hazard ratio.

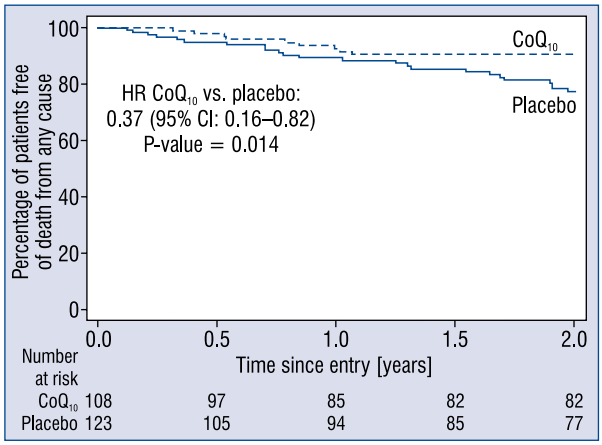

Figure 2. Estimates of the secondary outcome death from any cause in the placebo group (solid line) and the coenzyme Q_{10} (CoQ_{10}) group (dashed line); CI — confidence interval; HR — hazard ratio.

in 6MWT (325 m vs. 287 m) and a slightly higher mean LVEF (33% vs. 31%). The Europeans were more frequently treated with beta-blockers (88% vs. 73%), statins (57% vs. 36%) and anticoagulants (37% vs. 25%). Patients treated with device-based therapy in Q-SYMBIO were all European.

Event rate and treatment effects. The serum CoQ_{10} levels and overall event rates in the CoQ_{10} treated group of the European sub-population were similar or better than in the total population (Table 6). In the European sub-population, there was a significant improvement of 6% in LVEF compared to baseline ($p = 0.021$) in the CoQ_{10} group but no significant change in the placebo group ($p = 0.234$; Table 3). Whereas in the total population there were no significant between-group differences or changes from baseline in any of the echocardiographic measurements [12].

Discussion

Summary

The beneficial effect of CoQ_{10} in the landmark Q-SYMBIO study of 420 international patients was reflected in the more racially homogeneous, more intensively treated subgroup of 231 European patients in terms of a significant improvement in NYHA class and a significant risk reduction for the primary composite MACE endpoint and reductions in the secondary endpoints of all-cause mortality, cardiovascular mortality and hospitalization for HF. The improvements in major clinical endpoints were supported by a significant increase in LVEF in the European population which had not been found in the larger cohort [12]. It was concluded that the therapeutic efficacy of CoQ_{10} demonstrated in the original Q-SYMBIO study was confirmed and even enhanced in the European sub-population.

Despite a careful selection of patients and an apparently homogenous population in clinical studies there are inherent hidden factors in HF trials that may affect outcomes. These factors include ethnicity, medical preferences of physicians, financing of medical care and drug availability [13–15, 19]. This study aimed to investigate if the therapeutic efficacy of CoQ_{10} found in a total international population of Q-SYMBIO ($n = 420$) also applied to a more homogeneous European sub-population ($n = 231$). Compared to the total population of Q-SYMBIO, the European sub-population was slightly older, with a lower heart rate, a higher LVEF and a higher percentage with atrial fibrillation. Similar differences in baseline characteristics have recently been found in trials of chronic HF (PARADIGM-HF, EMPHASIS-HF) and acute HF (ASCEND-HF, ASTRONAUT) with patients enrolled from 5–6 global regions including Asia and Europe [14, 16, 20]. The European sub-population of Q-SYMBIO showed a higher adherence to guideline recommended medical and device therapies when compared to the entire study population. The Europeans were more frequently prescribed beta-blockers, statins and anticoagulants and less frequently digoxin. Furthermore, all patients receiving device-based therapy in Q-SYMBIO were European.

Table 5. Comparison of baseline characteristics in European and total population.

Characteristic	European population (n = 231)	Total population (n = 420)	P
Age [years]	64.8 ± 11	62.2 ± 12	0.007
Male sex	77%	73%	0.205
Weight [kg]	84.3 ± 17.8	77.5 ± 17	< 0.001
BMI [kg/m^2]	28.9 ± 6	28 ± 6	0.049
Heart rate [bpm]	73 ± 12	81 ± 15	< 0.001
Systolic BP [mmHg]	124 ± 20	123 ± 17	0.805
Diastolic BP [mmHg]	75 ± 11	78 ± 11	< 0.001
Sinus rhythm	62%	74%	0.003
Atrial fibrillation	26%	18%	0.019
Rhythm, other (pace)	12%	9%	0.138
Ischemic heart disease	66%	70%	0.333
Dilated cardiomyopathy	32%	27%	0.153
Valvular heart disease	3%	3%	1.000
Duration of HF [months]	41 ± 50	37 ± 41	0.271
NYHA class II	6%	3%	
NYHA class III	89%	87%	0.077
NYHA class IV	5%	9%	
Left ventricular EF [%], [range]	33 ± 12 [10–70]	31 ± 10 [10–70]	0.013
Left ventricular EDD [mm]	63 ± 11	65 ± 9	0.016
Left ventricular ESD [mm]	51 ± 13	54 ± 11	< 0.001
6MWT [m], [range]	325 ± 91 [25–525]	287 ± 98 [25–525]	< 0.001
Serum CoQ_{10} [μg/mL]	0.92 ± 0.07	0.92 ± 0.05	0.211
NT-proBNP [pg/mL]†	2399 ± 272, p50: 1196	1783 ± 276, p50: 782	0.051
Use of medications:			
ACEI/ARBs	91%	89%	0.476
Beta-blockers	88%	73%	< 0.001
Digoxin	32%	45%	0.002
Diuretics	84%	79%	0.138
Aldosterone antagonists	54%	56%	0.934
Statin derivatives	57%	36%	< 0.001
Anticoagulation	37%	25%	0.001
Diabetes treatment	26%	23%	0.441

Values are mean or number. †To convert values for NT-proBNP to picomoles per liter, divide by 8.457. ACE/ARB — angiotensin converting enzyme inhibitor/angiotensin receptor blocker; BMI — body-mass index; BP — blood pressure; CoQ_{10} — coenzyme Q_{10}; EDD — end-diastolic diameter; ESD — end-systolic diameter; EF — ejection fraction; HF — heart failure; NT-proBNP — N-terminal pro–B-type natriuretic peptide; NYHA — New York Heart Association; 6MWT — 6-min walk test

A sub-optimal use of guideline-directed medical therapy in Asian countries compared to Western countries has been described previously in registries for HF and recent large-scale HF trials [14, 20, 21]. Global differences in adherence to guideline-directed therapy in PARADIGM-HF and ASTRONAUT correspond to differences found in Q-SYMBIO including a higher rate in the prescription of beta-blockers, anticoagulation and a lower rate of digoxin in European populations compared to Asian-Pacific populations [16, 20]. A lower use of lipid-lowering agents such as statins in Asian countries is also well known [22]. Similarly, to Q-SYMBIO, analyses of PARADIGM-HF, ASTRONAUT and ASCEND-HF have demonstrated a markedly lower use of device-based therapy in Asian-Pacific regions compared to other regions, probably reflecting economic differences [16, 20, 21]. The more frequent prescription of anti-coagulants reflects the higher occurrence of

Table 6. Comparison of serum coenzyme Q_{10} (CoQ_{10}) and overall event rates and risk reduction at 2 years in the European and total population.

Endpoint	European sub-population				Total population			
	CoQ_{10} (n = 108)	Placebo (n = 123)	RRR	P	CoQ_{10} (n = 202)	Placebo (n = 218)	RRR	P
CoQ_{10}-S [μg/mL]	3.55	0.76		< 0.001	2.01	0.81		< 0.001
MACE	9%	27%	66%	0.001	15%	26%	43%	0.005
Death from any cause	9%	20%	53%	0.040	10%	18%	42%	0.036
Cardiovascular death	8%	17%	51%	0.052	9%	16%	43%	0.039
Hospitalization for HF	3%	13%	79%	0.007	8%	14%	41%	0.067

HF — heart failure; MACE — major adverse cardiovascular events; RRR — relative risk reduction

atrial fibrillation in the European sub-population of Q-SYMBIO. However, not all differences in medication can be explained by differences in baseline characteristics. Differences in medication and device therapy may be related to medical practice patterns, resources in medical care and perceptions of drug tolerability in Asian populations [21].

The findings in this analysis showing no major differences in outcomes in the European sub-population despite differences in medical therapy and baseline characteristics were in accordance with PARADIGM-HF and EMPHASIS. In contrast, regional differences in outcome have been found in acute HF trials ASTRONAUT and ASCEND-HF and may be a result of differences in the management and duration of hospitalization for acute HF patients having a greater impact on outcome [14].

The serum level of CoQ_{10} in the CoQ_{10} treated European sub-population remained constant and above 3 μg/mL throughout the study period (Tables 2, 6). In contrast, the serum level of CoQ_{10} in CoQ_{10} treated patients in the total population decreased from 3.01 ± 0.17 μg/mL at 3 months to 2.01 ± 0.20 μg/mL at 2 years (Table 6). This could indicate a problem with compliance in the non-European patient population towards the end of the study period. The higher serum levels of CoQ_{10} of the European HF patients during the full study period may have contributed to the slightly increased CoQ_{10} efficacy (increased LVEF; Tables 3, 6) compared with the efficacy found in the total population [12], despite the fact that the European cohort was better medicated and smaller sample size.

Current drug therapy for HF predominately targets the secondary consequences of the failing heart by blocking overactivated neurohormonal pathways. While this therapy provides some relief of symptoms, improves prognosis and prevents some degree of cardiac remodeling, it does not target the basic energy depletion of the failing myocardium [23]. Significantly decreased tissue levels of CoQ_{10} have been found in patients with failing hearts such as dilated cardiomyopathy, restrictive cardiomyopathy and toxic myocardial disease [9]. In patients with HF of mixed etiology, a deficiency of CoQ_{10} in serum and tissue is more pronounced in the severest stages of HF. After oral supplementation with CoQ_{10} of selected patients with cardiomyopathy undergoing repeat biopsies after 5 months of treatment, tissue deficiency was reduced significantly and this was accompanied by an improvement in clinical and hemodynamic parameters [9, 10, 24]. The therapeutic efficacy of CoQ_{10} is primarily ascribed to its important role as electron carrier in the electron transport chain and strong anti-oxidative properties thus increasing bioenergetics and preventing oxidative damage of the failing myocardium [25, 26]. Other beneficial actions of CoQ_{10} include stabilization of cell membranes and the mitochondrial membrane transition pore thus protecting the myocardium from apoptotic events [27]. Further evidence suggests that endothelial function is improved [28, 29] and cardiac contractility increased by CoQ_{10} [30, 31]. In concert, these actions by CoQ_{10} may halt the vicious cycle of HF and protect the myocardium from further deterioration and perhaps facilitate a potential for myocardial recovery [32].

Limitations of the study

In comparing the European subgroup with the main Q-SYMBIO group it was not possible to ascribe differences between European vs. non-European to ethnic or geographic differences. The main Q-SYMBIO group of 420 included 231 patients from Europe, 178 patients from Asia and 11 patients from Australia. Thus, it was not possible in this subgroup analysis to elucidate ethnic differences but rather to study and confirm the efficacy of CoQ_{10} in a sub-group where standard therapy was more closely applied. The present study was not

powered to assess between-population differences. Measurements of LVEF have a varying intra- and interobserver variance from 3% to 7% depending on how trained the observer is, nevertheless, an absolute improvement of 6% in LVEF is likely to be genuine and clinically relevant.

Conclusions

It was concluded that in the European subgroup of the Q-SYMBIO study the evidence of therapeutic efficacy of CoQ_{10} found in the original study was confirmed, despite higher adherence to guideline directed therapy than that of the whole group. In addition, CoQ_{10} therapy was associated with an increase in LVEF in the European population which had not been found in the larger cohort. This subgroup analysis provides confirmatory evidence for the conclusion of the original study that the treatment of patients with moderate to severe HF with CoQ_{10} in addition to standard therapy is safe, well tolerated and is associated with a reduction in symptoms, MACE and with improved survival.

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Long-term outcomes of patients with multivessel coronary artery disease presenting non-ST-segment elevation acute coronary syndromes

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Abstract

Background: *There is paucity of data concerning the optimal revascularization in patients with multivessel coronary artery disease (CAD) presenting non-ST-segment elevation acute coronary syndrome (NSTE-ACS). The aim was to evaluate long-term outcomes of patients with multivessel CAD presenting NSTE-ACS depending on the management after coronary angiography.*

Methods: *3,166 patients with NSTE-ACS hospitalized between 2006 and 2014 were screened. After exclusions, 1,342 patients were enrolled with multivessel CAD and were divided depending on their management after coronary angiography; the medical-only therapy group (n = 91), the percutaneous coronary intervention (PCI) group (n = 1,122), the coronary artery bypass grafting (CABG) group (n = 129). Propensity scores matching was used to adjust for differences in patient baseline characteristics.*

Results: *After propensity score analysis, 273 well-matched patients were chosen. Both before and after matching, patients treated with a medical-only therapy were burdened with the highest percentage of 24-month all-cause death and non-fatal MI in comparison to PCI and CABG groups, respectively. In the CABG group, ACS-driven revascularization rate was lowest. In the overall population, PCI (HR 0.33; 95% CI 0.20–0.53; p < 0.0001) and CABG (HR 0.54; 95% CI 0.31–0.93; p = 0.028) were independent factors associated with favorable 24-month prognosis. However, in a matched population only PCI was an independent predictor of long-term prognosis with a 63% decrease of 24-month mortality (HR 0.37; 95% CI 0.19–0.69; p = 0.0020).*

Conclusions: *In patients with multivessel CAD presenting with NSTE-ACS, medical-only management is related with adverse long-term prognosis in contrast to revascularization, which reduces 24-month mortality, especially among patients undergoing percutaneous intervention. Performance of PCI is an independent factor for improving long-term prognosis.* (Cardiol J 2019; 26, 2: 157–168)

Key words: non-ST-elevation myocardial infarction, percutaneous coronary intervention, coronary bypass grafts, multivessel coronary artery disease, long-term outcomes

Introduction

Multivessel coronary artery disease (CAD) is observed in 35–70% cases of non-ST-segment elevation acute coronary syndromes (NSTE-ACS) [1–4]. Moreover, multivessel CAD is one of the most common causes of higher risk for cardiovascular morbidity and mortality in this population [5, 6]. Although, an early invasive approach in patients with moderate-to-high risk is recommended, management of patients with confirmed multivessel CAD is controversial [7–9]. The guidelines suggest

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that the artery responsible for ischemia should be treated first [9, 10]. However, in the case of multivessel CAD, subsequent treatment strategies include percutaneous coronary intervention, (PCI), coronary artery bypass grafting (CABG) or medical-only therapy. Choice of treatment modality, completeness and optimal timing of revascularization (one- or multi-stage) of remaining lesions remains a contentious issue. Lack of detailed recommendations regarding optimal revascularization strategy is caused by a paucity of randomized trials and a small number of retrospective studies [11–14].

The main purpose of this study was to evaluate long-term outcomes of patients with multivessel CAD presenting NSTE-ACS. Therefore, an analysis was performed of clinical and angiographic status and the impact of treatment management on the incidence of 24-month all-caused death and identification of independent risk factors influencing the prognosis.

Methods

Study design

In this single-center prospective study, registry data of 3,166 consecutive patients with NSTE--ACS hospitalized from January 2006 to December 2014 were screened. Patients without invasive diagnostics during the acute phase of NSTE-ACS, with a history of CABG, with non-obstructive or single-vessel CAD were excluded from further analysis. Enrolled patients were divided into three groups depending on treatment after coronary angiography: medical-only therapy group — patients qualified for medical conservative treatment; PCI group — patients treated with PCI in the first instance; CABG group — patients treated CABG in the first instance.

The diagnosis and treatment of the study population were conducted in a highlyspecialized cardiology center with cardiac surgery facilities. Management of patients was based on current recommendations of the European Society of Cardiology (ESC) [9, 15, 16]. All patients qualified for invasive strategy have received acetylsalicylic acid and weight-adjusted unfractionated heparin. Coronary angiography was performed routinely from radial or femoral artery access depending on operator discretion. During invasive diagnostics, standard guidewires and catheters were used. After coronary angiography all decisions regarding method of treatment (medical management, PCI, CABG), in particular the use of stents, type of stent, type of cardiac surgery operation, number of grafts, periprocedural use of anticoagulants and antiplatelet drugs, and further revascularization were dependent on the decision of the operator or the Heart Team. In cases of recurrence of stenocardial symptoms associated with ST-T deviations, urgent coronary angiography was performed. Dual-antiplatelet therapy was endorsed for at least 12 months subsequent to hospitalization. Others drugs were prescribed in accordance with the ESC Guidelines [9, 15, 16]. The next stage of revascularization was routinely planned up to 3 months after index hospitalization. The adopted method of division into groups allowed the hybrid revascularization approach.

Data collecting and acquisition

Demographic, clinical and echocardiographic data regarding index hospital stay were collected by physicians and uploaded to the institutional database. Additionally, a retrospective analysis of coronary angiography, morphology and location of coronary artery lesions in all patients was conducted. 24-month follow-up data, including specific date of death, non-fatal myocardial infarction (MI) and acute coronary syndrome (ACS) driven revascularization was obtained from the official registry of the National Health Fund, guaranteeing complete data collection. Detailed data from further hospitalization planned within 3 month after discharge was also implemented to the institutional database. Follow-up data was available for whole study population.

This study was granted permission from the Institutional Review Board and University Bioethics Committee, and is in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments [17].

Definitions and endpoints

NSTE-ACS was diagnosed on the basis of (1) clinical presentation: i) prolonged (> 20 min) anginal pain at rest, ii) new onset (*de novo*) angina (Class II or III of the Classification of the Canadian Cardiovascular Society), iii) recent destabilization of previously stable angina with at least Canadian Cardiovascular Society Class III angina characteristics (crescendo angina), (2) the absence of ST-segment elevation consistent with an infarction of ≥ 2 mm in contiguous chest leads, ST-segment elevation of ≥ 1 mm in 2 or more standard leads, or a new left bundle branch block and (3) after exclusion of alternative causes of chest pain [9, 15, 16]. Subsequently, patients with NSTE-ACS were classified as having unstable angina (UA) or

non-ST-segment elevation myocardial infarction (NSTEMI) based on measured values of markers of myocardial necrosis in accordance with the Universal Definition of Myocardial Infarction [18]. Since 2009 high-sensitive cardiac troponin T was measured in the institutional central laboratory. Multivessel CAD was defined as hemodynamically significant stenosis in left main (LM) or in at least two major epicardial territories or in their major branches (left anterior descending [LAD], left circumflex or right coronary artery system) with a diameter ≥ 2.0 mm as determined by visual assessment with on-line quantitative coronary angiography using orthogonal views [19]. As hemodynamically significant ≥ 50% diameter stenosis in LM or proximal segment of LAD and ≥ 70% diameter stenosis in other segments were also considered. Angiographic success was defined as the achievement of a minimum stenosis diameter reduction to < 20% in the presence of TIMI flow 3 grade.

The primary outcome measure included the occurrence of 24-month all-cause death. The secondary endpoints were non-fatal recurrent myocardial infarction (MI), ACS-driven unplanned revascularization and stroke at 24 months. Non-fatal MI was defined as an ischemic event that met ESC/American College of Cardiology criteria for MI and were clearly clinically separate from the baseline ACS at the time of admission [18]. ACS-driven repeat revascularization was defined as additional, unplanned angioplasty or CABG, performed as an urgent procedure because of acute ischemic symptoms [19]. Stroke was defined as an ischemic event that was in accordance with European Stroke Organization guidelines [20].

Statistical analysis

Statistical analysis included a comparison of baseline, angiographic and procedural characteristics, and the incidence of cardiovascular events during 24-month follow-up. The analyzed variables are expressed as numbers and percentages. The distribution normality was verified using the Shapiro-Wilk test. Continuous variables were summarized using arithmetic mean with standard deviation (SD) for data following normal distribution or median with quartile 1 and 3 (Q1–Q3) for data demonstrating non-normal distribution. The analysis of variance (ANOVA) test for comparison of continuous parameters with normal distribution was performed, whereas the Kruskal-Wallis ANOVA rank test for parameters with non-normal distribution was used. Categorical variables were compared using the χ^2 test with the Pearson's modification or with the Yates correction if the expected number of observations was less than 5. All-cause mortality, non-fatal MI, ACS-driven revascularization and stroke in 24-month follow-up for all patients were analyzed using the Kaplan-Meier method with log-rank test. To minimize the confounding impact of risk factors affecting 24-month outcomes. A propensity score analysis was performed to adjust for differences in patient baseline characteristics. First, logistic regression was performed to score all patients according to treatment (medical-only therapy vs. PCI; medical-only therapy vs. CABG), used as covariates the clinical and procedural parameters that were clinically relevant for the endpoint: age (years), gender (male/female), diabetes mellitus, prior MI, ST-segment deviation, left ventricular ejection fraction, triple-vessel CAD and chronic total occlusion. In the next stage, analyses were performed on two matched groups (medical-only therapy vs. PCI and medical-only therapy vs. CABG), stratified into pairs to account for propensity score matching. The nearest neighbor matching was used. Both before and after propensity score matching, the Cox proportional hazards model was performed. Factors were analyzed by stepwise backward elimination ($p < 0.3$ for entry into the model, $p < 0.05$ to remain in the model). The independence of factors were verified by interactions testing. Results were summarized as hazard ratio (HR) with 95% confidence interval (CI). A two-sided p-value < 0.05 was considered significant. The STATISTICA 10 software (StatSoft Inc., Tulsa, Oklahoma) was used for all calculations.

Results

During an observation period from 2006 to 2014, a total of 3,166 patients with NSTE-ACS were analyzed (Fig. 1). After exclusions, among patients with multivessel CAD, in 91 patients medical-only treatment was implemented while in the remaining 1,251 patients revascularization was performed. Of these, 1,122 patients underwent PCI and 129 patients CABG. The average age of the study population was 66.9 ± 10.9 years, 68.0% were males, and the definitive diagnosis of MI was recognized in 64.2%. Baseline characteristics and results of additional testing of the study groups are summarized in Table 1. In general, the medical-only treatment group had the worst clinical profile with the highest GRACE score results. The post-hoc analysis showed that patients from

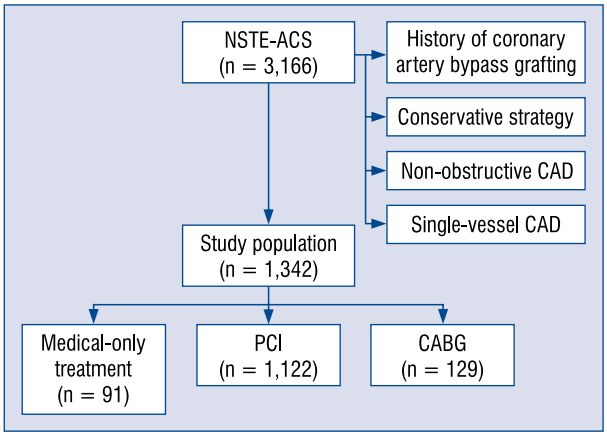

Figure 1. Study design; CABG — coronary artery bypass grafting; CAD — coronary artery disease; NSTE-ACS — non-ST-segment elevation acute coronary syndromes; PCI — percutaneous coronary intervention.

the PCI group in comparison with CABG group had significantly more frequently final NSTEMI diagnosis, higher troponin T ($p < 0.0001$), glucose level on admission ($p = 0.0029$), lower level of left ventricular ejection fraction ($p = 0.0033$), while less often arterial hypertension ($p = 0.012$) and peripheral artery disease ($p = 0.026$). Overall, the GRACE Risk in PCI in comparison with CABG group was higher ($p = 0.036$). Angiographic and procedural characteristics are presented in Table 2. Patients qualified to medical-only treatment and to cardiac surgery demonstrated more advanced severity of coronary disease when compared to patients treated with PCI. Overall, the rate of patients undergoing hybrid revascularization was 5.7% (6.1% in PCI group and 2.3% in CABG group). Approximately half of patients from CABG group underwent complete anatomic revascularization after 6-month from discharge, whereas in PCI group this proportion accounted for approximately one-third of patients.

After propensity score matching of the study population group, 273 patients were selected. Patients in medical-only therapy and PCI groups had lower left ventricular ejection fraction in comparison to CABG patients. Also, the overall GRACE score was higher in medical-only therapy than in CABG group. Left main disease was more frequent in medical-only therapy and CABG than in PCI group. The other differences in baseline clinical characteristics and angiography were reduced with nonsignificant p value.

Table 3 contains the in-hospital, early and long-term outcomes. Kaplan-Meier curves for

Table 1. Baseline characteristics of study population and matched cohort.

Factor	Study population (n = 1,342)			P	Matched group (n = 273)			P
	Medical-only treatment (n = 91)	PCI (n = 1,122)	CABG (n = 129)		Medical-only treatment (n = 91)	PCI (n = 91)	CABG (n = 91)	
Age (years ± SD)	68.4 ± 10.1	66.8 ± 10.5	66.8 ± 9.4	0.35	68.4 ± 10.1	68.6 ± 10.0	68.6 ± 8.8	0.93
Male	64.8%	67.7%	73.6%	0.29	64.8%	65.9%	68.1%	0.89
Diagnosis of NSTEMI	57.1%	67.6%	41.1%	< 0.0001	57.1%	54.9%	48.3%	0.46
Arterial hypertension	83.3%	75.3%	85.3%	0.011	83.3%	82.4%	87.9%	0.55
History of CAD	68.1%	57.0%	62.8%	0.065	68.1%	70.3%	70.3%	0.93
Prior MI	51.1%	39.0%	42.6%	0.051	51.1%	46.1%	53.8%	0.80
Prior PCI	29.6%	31.3%	20.2%	0.033	29.4%	35.2%	25.3%	0.35
Atrial fibrillation	12.8%	10.4%	10.1%	0.74	12.8%	16.5%	11.0%	0.54
Peripheral artery disease	21.6%	13.2%	20.2%	0.011	21.6%	28.6%	19.8%	0.34
Prior stroke	7.7%	7.2%	9.3%	0.67	7.7%	14.3%	13.2%	0.33
Diabetes mellitus	51.1%	37.3%	39.5%	0.024	51.1%	54.9%	50.6%	0.97
Diabetes mellitus insulin-treatment	22.7%	16.6%	18.6%	0.29	22.7%	19.8%	22.0%	0.88

Table 1 (cont.). Baseline characteristics of study population and matched cohort.

Factor	Study population (n = 1,342)			P	Matched group (n = 273)			P
	Medical-only treatment (n = 91)	PCI (n = 1,122)	CABG (n = 129)		Medical-only treatment (n = 91)	PCI (n = 91)	CABG (n = 91)	
Chronic kidney disease	11.8%	9.4%	5.4%	0.22	11.8%	10.0%	6.7%	0.42
Dyslipidemia	67.7%	67.5%	67.4%	0.99	67.7%	71.4%	74.7%	0.59
Obesity	29.5%	26.7%	18.6%	0.10	29.5%	34.1%	23.1%	0.26
COPD	9.9%	4.9%	2.3%	0.032	9.9%	6.6%	3.3%	0.20
History of cigarette smoking	45.1%	42.7%	43.4%	0.89	45.1%	35.2%	45.0%	0.30
Current smoking	18.7%	17.6%	17.0%	0.95	18.7%	22.0%	19.8%	0.85
Familiar history of MI	24.5%	22.6%	27.1%	0.49	24.5%	19.8%	24.2%	0.70
Chest pain*	89.0%	91.2%	90.7%	0.62	89.0%	90.1%	89.0%	0.96
Killip class III*	4.4%	2.4%	0.0%	0.11	4.4%	6.6%	0.0%	0.055
Killip class IV*	0.0%	1.4%	0.0%	0.21	0.0%	0.0%	0.0%	–
Heart rate* [bpm ± SD]	82 ± 19	78 ± 16	78 ± 15	0.13	82 ± 19	80 ± 14	80 ± 16	0.60
Systolic blood pressure* [mmHg ± SD]	143 ± 28	147 ± 29	147 ± 30	0.32	143 ± 28	147 ± 30	146 ± 33	0.76
Diastolic blood pressure* [mmHg ± SD]	84 ± 16	86 ± 16	85 ± 16	0.49	84 ± 16	84 ± 18	85 ± 17	0.83
ST-segment deviations*	57.6%	40.9%	44.7%	0.0061	57.6%	61.8%	51.5%	0.43
LBBB*	11.0%	6.1%	5.3%	0.20	11.0%	5.3%	7.4%	0.29
RBBB*	1.3%	5.6%	4.3%	0.21	1.2%	10.5%	4.4%	0.40
BMI [kg/m^2 ± SD]	28.5 ± 4.9	28.7 ± 4.8	28.4 ± 6.1	0.82	28.5 ± 4.9	28.3 ± 4.9	28.9 ± 6.8	0.73
Cardiac troponin T*# [ng/mL] (Q1–Q3)	0.11 (0.02–0.53)	0.10 (0.02–0.50)	0.05 (0.01–0.25)	0.011	0.11 (0.02–0.53)	0.10 (0.01–0.61)	0.09 (0.02–0.46)	0.94
Elevated cardiac troponin T*#	76.7%	77.9%	67.1%	0.078	76.7%	74.6%	79.7%	0.75
WBC* [thousand/μL] (Q1–Q3)	8.5 (6.8–11.4)	8.4 (6.9–11.4)	8.1 (6.8–9.6)	0.36	8.5 (6.8–11.4)	8.6 (6.5–10.6)	8.3 (7.0–10.4)	0.51
Hemoglobin* [mmol/L ± SD]	8.5 ± 1.0	8.5 ± 1.0	8.4 ± 0.9	0.59	8.5 ± 1.0	8.4 ± 1.0	8.3 ± 0.9	0.18
Glucose* [mmol/L] (Q1–Q3)	6.6 (5.8–9.3)	6.6 (5.5–8.6)	6.0 (5.0–8.1)	0.023	6.6 (5.8–9.3)	6.8 (5.6–9.4)	6.4 (5.0–8.8)	0.31
Serum creatinine* [μmol/L] (Q1–Q3)	88 (72–112)	84 (69–103)	86 (71–102)	0.51	88 (72–112)	84 (69–114)	91 (76–104)	0.67
eGFR* [mL/min/1.73 m^2] (Q1–Q3)	69 (49–86)	78 (58–97)	76 (58–95)	0.049	69 (49–86)	76 (54–100)	71 (56–86)	0.70
LVEF* [% ± SD]	38.0 ± 11.6	43.3 ± 10.4	46.1 ± 9.7	< 0.0001	38.0 ± 11.6	39.7 ± 11.2	43.5 ± 9.0	0.0028
LVEF < 35%*	47.6%	24.3%	14.4%	< 0.0001	47.6%	38.2%	16.7%	0.0002
GRACE scale [points] (Q1–Q3):	137 (115–154)	122 (103–143)	119 (97–133)	< 0.0001	137 (115–154)	133 (114–149)	129 (107–141)	0.035
> 140 points	46.9%	28.7%	15.1%	< 0.0001	46.9%	37.4%	27.6%	0.0093
109–140 points	31.0%	39.5%	50.0%	0.016	31.0%	40.7%	46.0%	0.074
≤ 108 points	22.1%	31.7%	34.9%	0.076	22.1%	22.0%	26.4%	0.70

*On admission; #Since 2009 high-sensitive cardiac troponin T was measured.
BMI — body mass index; CABG — coronary artery bypass grafting; CAD — coronary artery disease; COPD — chronic obstructive pulmonary disease; eGFR — estimated glomerular filtration rate; LBBB — left bundle branch block; LVEF — left ventricular ejection fraction; MI — myocardial infarction; NSTEMI — non-ST-segment elevation myocardial infarction; PCI — percutaneous coronary intervention; Q1–Q3 — quartile 1 and quartile 3; RBBB — right bundle branch block; SD — standard deviation; WBC — white blood cells

Table 2. Angiographic and procedural characteristics of study population and matched cohort.

Factor	Study population (n = 1,342)			P	Matched group (n = 273)			P
	Medical-only treatment (n = 91)	PCI (n = 1,122)	CABG (n = 129)		Medical-only treatment (n = 91)	PCI (n = 91)	CABG (n = 91)	
Triple-vessel CAD	52.0%	39.1%	59.7%	< 0.0001	52.0%	60.4%	54.9%	0.56
LM CAD	25.2%	8.8%	34.9%	< 0.0001	25.2%	7.7%	33.0%	0.0001
Chronic total oclussion	70.4%	45.2%	49.6%	< 0.0001	70.4%	71.4%	60.4%	0.22
PCI during initial hospitalization	–	99.2%	3.7%	< 0.0001	–	98.9%	–	–
Drug eluting stent	–	27.7%	–	–	–	34.4%	–	–
Angiographic success	–	91.3%	–	–	–	88.9%	–	–
Performed PCI after discharge	–	23.4%	2.3%	< 0.0001	–	16.5%	1.1%	0.0001
CABG during initial hospitalization	–	–	37.9%	–	–	–	31.9%	–
Performed CABG after discharge	–	6.1%	62.1%	< 0.0001	–	9.9%	68.1%	< 0.0001
Time from admission to first procedure [days] (Q1–Q3)	–	1 (1–1)	29 (11–49)	< 0.0001	–	1 (1–2)	28 (10–46)	< 0.0001
Complete revascularization	–	34.1%	51.9%	< 0.0001	–	20.9%	51.6%	< 0.0001

CABG — coronary artery bypass grafting; CAD — coronary artery disease; LM — left main; PCI — percutaneous coronary intervention; Q1–Q3 — quartile 1 and 3

study groups are presented in Figure 2. A total percentage of 12- and 24-month all-cause death in the overall study population was 12.8% and 18.7%, respectively. Patients treated with medical-only therapy were burdened with the highest percentage of 12- and 24-month all-cause death. Moreover, the highest rate of non-fatal MI in those patients was observed. In the CABG group, ACS-driven revascularization rate was the lowest. After propensity score matching, there were no differences in the incidence of 12-month events between analyzed groups. At 24 months, the medical-only treatment was associated with the highest occurrence of all-cause death and non-fatal MI, while in PCI group had the highest rate of ACS-driven revascularization.

The Cox proportional hazards model before (A) and after (B) propensity score matching is presented in Figure 3. In the study population, PCI and CABG were independent factors of improved 24-month prognosis. However, in matched population only PCI was an independent predictor of 24-month prognosis with reduction of 24-month mortality by 63%.

Discussion

The vast majority of contemporary studies comparing treatment strategy of multivessel CAD were performed in patients with stable angina [21––23]. Multicenter, randomized trials comparing PCI to CABG, encompassed from 13% to 91% patients with UA or recent MI [22]. In NSTE-ACS population, except for one single-center trial comparing an optimal timing of staged multivessel intervention [13], to date no prospective randomized clinical trial has been conducted to evaluate the treatment modality of multivessel CAD. Moreover, there is only a limited number of data obtained from one subanalysis of randomized trial and few retrospective studies [11, 12, 14, 24–26]. The optimal treatment method in overall as well as in particular subgroups of patients with NSTE-ACS is unclear. Therefore, the decision to conduct an assessment of treatment of multivessel CAD in real-world patients presenting with NSTE-ACS was undertaken.

In the present study comprising 3,166 patients with NSTE-ACS, the percentage of multivessel CAD without prior CABG was more than 42%. The present results are similar to those previously reported for NSTE-ACS patients, where occurrence of multivessel CAD ranged from 35% to 70% [1–4]. Also, baseline clinical and angiographic characteristics of the patients appears to be

Table 3. In-hospital, 30-day, 12-month and 24-month outcomes of study population and matched cohort.

Factor	Study population (n = 1,342)			P	Matched group (n = 273)			P
	Medical-only treatment (n = 91)	PCI (n = 1,122)	CABG (n = 129)		Medical-only treatment (n = 91)	PCI (n = 91)	CABG (n = 91)	
In-hospital outcomes:*								
All-cause death	5.5%	2.8%	3.9%	0.29	5.5%	4.4%	4.4%	0.92
Non-fatal MI	0.0%	1.3%	0.8%	0.51	0.0%	0.0%	1.1%	0.37
TVR#	0.0%	2.6%	0.0%	0.065	0.0%	3.3%	0.0%	0.48
Stroke	1.1%	0.4%	2.8%	0.0046	1.1%	1.1%	3.3%	0.44
Cardiogenic shock	0.8%	2.9%	0.0%	0.093	1.1%	2.2%	0.0%	0.36
Pulmonary edema	8.7%	4.5%	0.0%	0.0086	8.7%	8.7%	1.1%	0.046
Blood transfusion	4.4%	5.5%	3.7%	0.63	4.4%	8.8%	3.3%	0.23
Cardiac arrest	5.5%	3.4%	0.9%	0.22	5.5%	4.4%	0.0%	0.090
30-day:								
All-cause death	11.0%	4.0%	4.6%	0.0028	11.0%	4.4%	5.5%	0.098
Non-fatal MI	2.2%	2.3%	1.7%	0.94	2.2%	1.1%	1.1%	0.78
ACS-driven revascularization	1.1%	3.9%	0.0%	0.028	1.1%	3.3%	0.0%	0.17
Stroke	3.3%	0.4%	2.8%	0.0005	3.3%	1.1%	3.3%	0.82
12-month:								
All-cause death	25.3%	11.7%	11.1%	0.0010	25.3%	14.3%	14.3%	0.083
Non-fatal MI	14.3%	8.3%	4.6%	0.025	14.3%	12.1%	4.4%	0.070
ACS-driven revascularization	8.8%	10.1%	1.7%	0.019	8.8%	14.3%	4.4%	0.068
Stroke	4.4%	1.7%	4.6%	0.034	4.4%	3.3%	4.4%	0.91
24-month:								
All-cause death	42.1%	16.5%	20.5%	< 0.0001	42.1%	23.0%	22.0%	0.0041
Non-fatal MI	19.3%	11.1%	4.7%	0.0035	19.3%	14.9%	5.5%	0.020
ACS-driven revascularization	12.5%	12.7%	4.7%	0.031	12.5%	19.5%	4.4%	0.0080
Stroke	3.4%	3.0%	7.1%	0.062	4.4%	3.4%	7.7%	0.31

*during index hospitalization; ACS — acute coronary syndrome; CABG — coronary artery bypass grafting; MI — myocardial infarction; PCI — percutaneous coronary intervention; TVR — target vessel revascularization

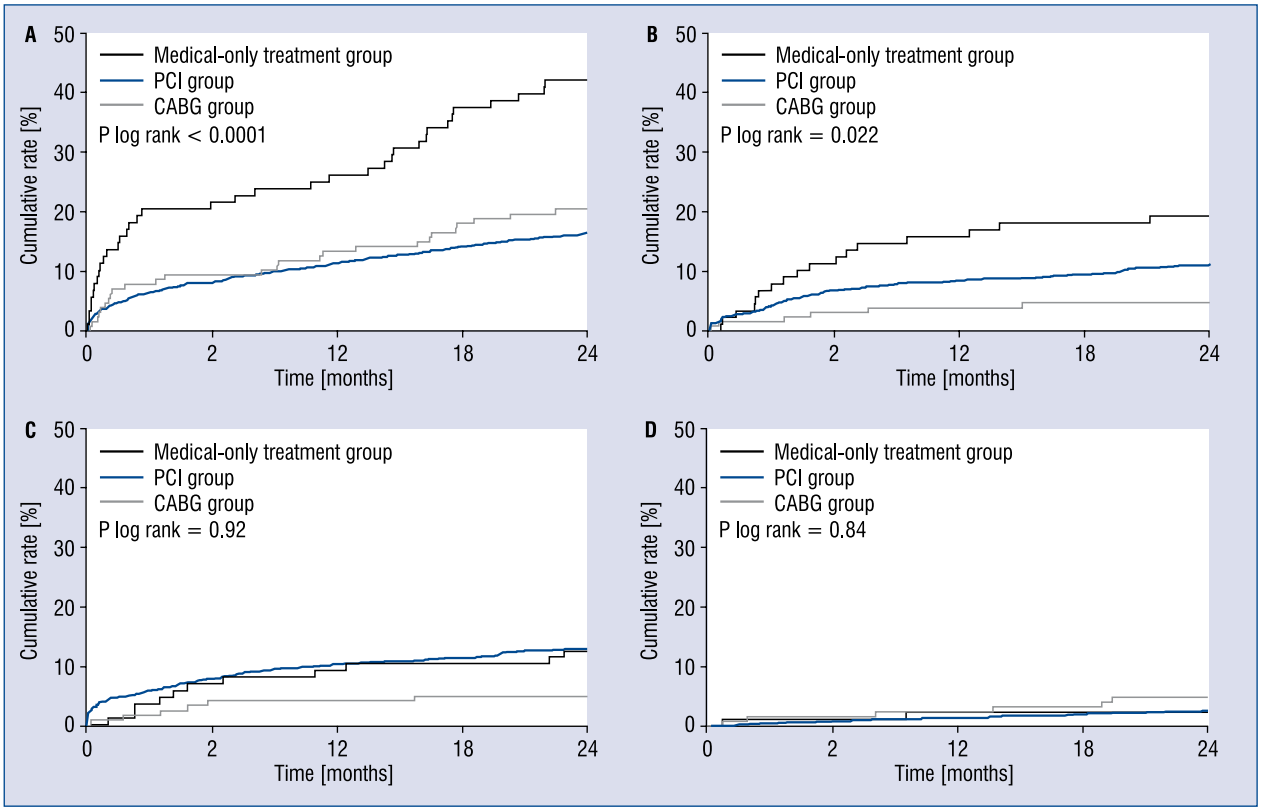

Figure 2. Kaplan-Meier survival curves for 24-month rates of all-cause death (**A**), non-fatal myocardial infarction (**B**) acute coronary syndromes-driven revascularization (**C**) and stroke (**D**) in study groups; CABG — coronary artery bypass grafting; PCI — percutaneous coronary intervention.

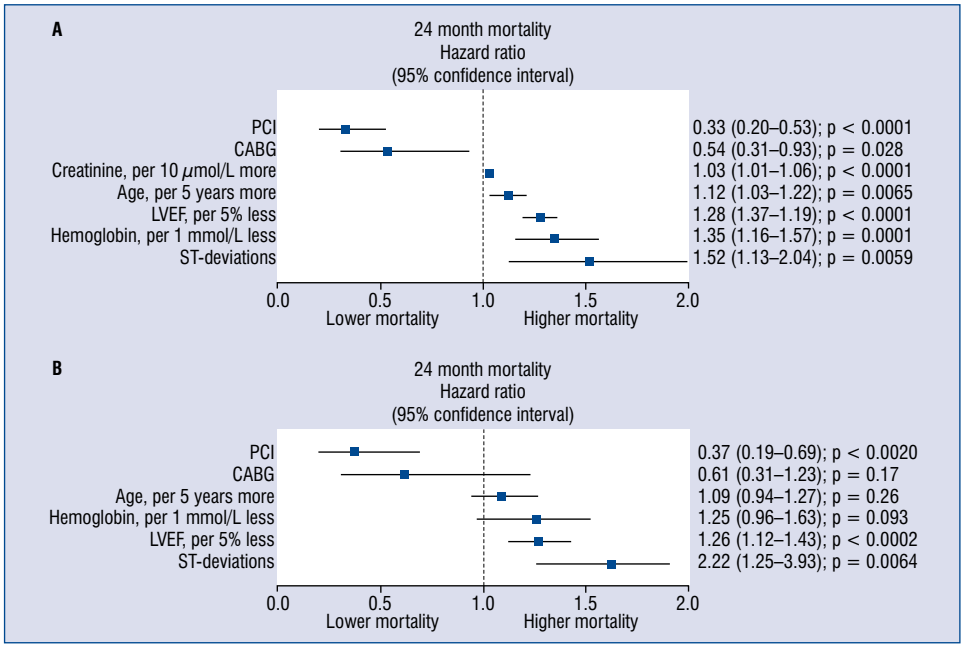

Figure 3. Forest plot of independent predictors of 24-month all-cause mortality in the study population (**A**) and in a matched cohort (**B**); CAD — coronary artery disease; CI — confidence interval; LVEF — left ventricular ejection fraction; PCI — percutaneous coronary intervention.

comparable to other registries, this demonstrates a good reflection of the present patients to the general population of NSTE-ACS [11, 12, 25]. In this study, patients treated invasively constituted less than 84%, surgical treatment was performed in 10% and in remaining patients the medical-only treatment was implemented. Gierlotka et al. [27] found that the rates of revascularization among Polish patients with NSTEMI shows an upward trend with contemporary use of PCI in more than 55%, and CABG in more than 10% patients. In subanalysis of ACUITY trial, designed to compare two methods of revascularization in multivessel CAD, patients undergoing PCI accounted for 78%, while CABG group consisted of 22% of study population [14]. Also, in other studies PCI was the most common method of treatment for multivessel CAD in NSTE-ACS [24–26, 28].

Early and long-term outcomes in the present analysis have shown that patients treated conservatively after coronary angiography are characterized by the worst prognosis. This result is intelligible in terms of current state of the art of management in NSTE-ACS [9, 29]. Qualification for medical-only treatment after diagnostic coronary angiography may be result of anatomical infeasibility of revascularization (i.e. rates of chronic total occlusions) and/or severe clinical status of patients [30]. The long-term outcomes were similar in PCI and CABG groups, except for higher frequency of ACS-driven revascularization in PCI group. There were no differences in the occurrence of stroke. In virtually all clinical trials, CABG was associated with higher rates of stroke in comparison with PCI [31]. The results of ACUITY trial showed that invasive treatment may be associated with lower incidence of non-fatal periprocedural MI, stroke and major bleeding, while CABG with lower occurrence of recurrent ischemia [14]. After propensity score matching analysis, early and long-term mortality in patients treated with PCI was similar to CABG group. However, an insignificant, but numerically higher incidence of the composite endpoint (25% vs. 19%; $p = 0.053$) was observed, which was mainly driven by a meaningfully higher percentage of unplanned repeat revascularization (12% vs. 0.2%; $p < 0.001$). A similar correlation demonstrating comparable efficacy of PCI and CABG in NSTE-ACS has been demonstrated in the issue of unprotected LM coronary artery [32, 33], a proximal segment of LAD [34] and in patients with multivessel CAD and diabetes mellitus [35]. On the other hand, in the MILESTONE Registry, immediate PCI was associated with lower long-term mortality risk compared with surgical revascularization, especially in subgroups at high clinical risk [26]. Importantly in the present study, after adjusting for factors from baseline and angiographic characteristics, the performance of PCI was an independent predictor of improved prognosis in 24-month follow-up. These meaningful outcomes are in accordance with the expert opinions that after identification a culprit vessel during coronary angiography, PCI should be the first choice procedure in the treatment of NSTE-ACS. After PCI of culprit vessel, further decisions regarding revascularization of non-ischemia-related vessels should be carried out after Heart Team consultation or based on the locally adopted proceedings protocols. PCI should also be recommended in the case of an occurrence of multiple lesions responsible for the manifestation of NSTE-ACS [36].

It is well documented that most benefits from an invasive strategy and subsequent PCI refers to patients undergoing intervention respectively in 24 (high risk) or 72 (moderate risk) hours from admission to hospital [9]. However, another important issue in multivessel CAD is optimal timing of revascularization in vessels other than the culprit vessel. There is widespread agreement of experts that in stable clinical status after intervention in the artery responsible for NSTE-ACS, treatment decisions regarding other stenosed vessels may be based on recommendations for stable CAD. In patients with severe, multivessel CAD, the preferred modality of treatment recommended by ESC is CABG. Nevertheless, outcomes of SYNTAX and EXCEL trials indicate that, the use of PCI as an alternative to cardiac surgery may be applied in patients with low-to-moderate SYNTAX score [21, 37, 38]. In the present study, more than a quarter of patients in PCI group was scheduled for the next stage of revascularization after discharge, whereas in 62% patients of CABG group, the operation was performed during further hospitalization. The results of retrospective studies and their meta-analyzes suggest that performing multivessel PCI during index hospitalization in patients presenting with NSTE-ACS may improve a long-term prognosis [11, 12]. Sardella et al. [13] in SMILE Trial has demonstrated that one-stage multivessel PCI is superior to postponed intervention. Due to a lack of randomized trials, optimal time frames of performance of CABG in NSTE-ACS patients are unclear. In accordance with expert consensus and results of clinical registries, CABG should be implemented after 48–72 hours after performance of culprit vessel PCI, except for patients

with ongoing myocardial ischemia, hemodynamic instability or very-high-risk coronary anatomy when there should be no delay with an operation [39]. However, the final decision should be taken by the Heart Team on the basis of clinical status and severity of CAD.

The previous data indicate that more complete revascularization of multivessel CAD may be associated with lower frequency of adverse events, particularly repeat urgent revascularization when compared to treatment limited only to the artery responsible for NSTE-ACS manifestation [11, 12]. Herein was found that the percentage of patients who underwent complete revascularization within 6 months after diagnosis of NSTE-ACS was more than 34% in PCI group and more than 50% in the CABG group. Similarly, a meta-analysis of retrospective studies proved that performance of multivessel PCI results in a reduction of long-term composite endpoint, mainly due to lower incidence of ischemia-driven revascularization. Data above indicate the need for complete revascularization in patients with multivessel CAD, if anatomical factors and the clinical condition allows.

Limitations of the study

This study was a single-center, retrospective study with potential selection biases. After coronary angiography, the further treatment decisions to perform PCI or CABG was at the operator or Heart Team discretion. The results of SYNTAX score and EuroScore were not available. Multivariate analysis may be biased because of the potential effect of confounding predictors that were not accessible in this database. A longer period of follow-up is required for more complete evaluation of PCI and CABG treatment.

Conclusions

In summary, presented results indicate that more than 90% of patients with multivessel CAD in the course of NSTE-ACS underwent coronary revascularization, of which the vast majority were treated by percutaneous intervention. The highest morbidity, risk and severe of CAD was observed in patients qualified for medical-only treatment. Also, medical-only management was related worse long-term prognosis in contrast to revascularization, which reduces 24-month mortality. In addition to known factors associated with higher mortality, the use of PCI is an independent factor for improving prognosis of 24-month follow-up. Optimal revascularization method in multivessel CAD and NSTE-ACS patients requires multicenter and randomized trials in the future.

Conflict of interest: None declared

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Predictive value of CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores for failed reperfusion after thrombolytic therapy in patients with ST-segment elevation myocardial infarction

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Abstract

Background: *Thrombolytic therapy is recommended for patients with acute ST-segment elevation myocardial infarction (STEMI) who cannot undergo primary percutaneous coronary intervention within the first 120 min. The aim of this study was to demonstrate the value of CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores in predicting failed reperfusion in STEMI patients treated with thrombolytic therapy.*

Methods: *A total of 537 consecutive patients were enrolled in the study; 139 had failed thrombolysis while the remaining 398 fulfilled the criteria for successful thrombolysis. Thrombolysis failure was defined with the lack of symptom relief, < 50% ST resolution-related electrocardiography within 90 min from initiation of the thrombolytic therapy, presence of hemodynamic or electrical instability or in-hospital mortality. CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores, which incorporate hyperlipidemia, smoking, switches between female and male gender, were previously shown to be markers of the severity of coronary artery disease (CAD).*

Results: *History of hypertension, diabetes mellitus, hyperlipidemia, heart failure, smoking, and CAD were significantly common in failed reperfusion patients (for all; $p < 0.05$). For prediction of failed reperfusion, the cut-off value of CHA_2DS_2-VASc* score was *≥ 2 with a sensitivity of 80.90% and a specificity of 41.01% (area under curve [AUC]* 0.660*; 95% confidence interval [CI] 0.618–0.700; $p < 0.001$) and the cut-off value of CHA_2DS_2-VASc-HS* score was *≥ 3 with a sensitivity of 76.13% and a specificity of 67.63% (AUC 0.764; 95% CI 0.725–0.799; $p < 0.001$). The CHA_2DS_2-VASc-HS score was found to be statistically and significantly better than CHA_2DS_2-VASc score to predict failed reperfusion ($p < 0.001$).*

Conclusions: *The findings suggest that the CHA_2DS_2-VASc and especially CHA_2DS_2-VASc-HS scores could be considered as predictors of risk of failed reperfusion in STEMI patients.* (Cardiol J 2019; 26, 2: 169–175)

Key words: CHA_2DS_2-VASc score, thrombolytic therapy, failed thrombolysis

Introduction

Acute reperfusion, performed either with thrombolytic therapy or primary percutaneous coronary intervention (PCI), is the mainstay of treatment for patients experiencing an acute ST-segment elevation myocardial infarction (STEMI). Although contemporary guidelines for

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acute STEMI patients recommend primary PCI as the preferred reperfusion strategy, most patients do not present to a PCI-capable hospital [1]. Thus, thrombolysis remains the treatment of choice for STEMI patients when a PCI cannot be performed within the first 120 min or it is delayed due to patient transfer. A routine coronary angiography is recommended 2–24 h after thrombolytic therapy, and a rescue PCI should be performed when thrombolytic therapy fails [1]. Reperfusion fails in almost one third of patients receiving thrombolytic therapy, and these patients require a rescue PCI [2, 3]. Estimating the risk of reperfusion failure in individual patients before initiation of thrombolytic therapy may be helpful to determine the optimal treatment strategy especially for patients admitted to non-PCI capable hospitals. Previous studies reported that parameters such as red cell distribution width, mean platelet volume, platelet distribution width and C-reactive protein (CRP) on admission may be helpful in predicting failed reperfusion [4–7]. However, according to available literature, there is currently no scoring system which can be used to predict failed reperfusion in STEMI patients to whom thrombolytic therapy is given. The CHA_2DS_2-VASc score is traditionally used for thromboembolic risk stratification in atrial fibrillation (AF) patients [8]. The components of the CHA_2DS_2-VASc score, namely hypertension (HT), diabetes mellitus (DM), old age, and heart failure, were also shown to be risk factors for poor clinical outcomes in cardiovascular diseases. Recent studies demonstrated that CHA_2DS_2-VASC score can also predict poor clinical outcomes in stable coronary artery disease (CAD) and acute coronary syndrome, irrespective of the presence of AF [9, 10]. Cetin et al. [9] demonstrated that $CHADS_2$, CHA_2DS_2-VASc and the newly defined CHA_2DS_2-VASc-HS scores can predict the severity of CAD in diagnostic coronary angiography, and it was reported that CAD severity increased with higher scores. In that study, the authors replaced the female gender in CHA_2DS_2-VASc score with male gender, and they also incorporated hyperlipidemia and smoking as risk factors for the development of CAD. The present study aimed to demonstrate the value of CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores in predicting failed reperfusion in STEMI patients treated with thrombolytic therapy.

Methods

In the present study, data was obtained from 537 consecutive STEMI patients, who were admitted to our tertiary-care center from January 2008 to April 2015 and who received thrombolytic therapy based on a clinical decision of the attending cardiologist.The study was designed retrospectively, and complied with the principles of the Declaration of Helsinki and the local ethics committee approved the study protocol. The thrombolytic agent administered was a tissue plasminogen activator (t-PA; alteplase) or tenectoplase or reteplase. The choice of thrombolytic agent was based on the decision of the treating physician according to recommended doses [11]. Failed thrombolysis was defined according to the following criteria; lack of symptom relief (worsening ischemia or persistent chest pain), presence of hemodynamic or electrical instability, ST-segment resolution-related electrocardiography leads within 90 min from the initiation of the thrombolytic therapy, and in-hospital mortality. Totally 139 patients were defined as failed reperfusion according to these criteria. Clinical and demographic characteristics including age, gender, history of DM, HT, hyperlipidemia, current cigarette smoking, family history of premature CAD, and chronic heart failure were obtained from medical history, physical examination, electrocardiographic findings, laboratory data and digital and/or non-digital hospital records. low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride measurements, and renal function tests were performed by standardized laboratory methods. LDL-C concentrations were calculated using the Friedewald formula [12]. Hypertension was defined as repeated measurements of systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or chronic treatment with antihypertensive medications. Type 2 DM was defined as a previous diagnosis and/or a fasting blood glucose of > 126 mg/dL or the use of anti-diabetic medications. Hyperlipidemia was defined by a total cholesterol level above 200 mg/dL or use of lipid-lowering medications. Cigarette smoking was defined as smoking ≥ 1 cigarettes a day for at least 1 year, without an attempt to quit. Family history was defined as the presence of heart disease or sudden cardiac death in a male first-degree relative aged < 55 years or in a female first-degree relative aged < 65 years. Chronic heart failure was defined as reduced left ventricular ejection fraction ($< 40\%$).

The CHA_2DS_2-VASc nomenclature represents heart failure (C), hypertension (H), age ≥ 75 years (A_2), diabetes mellitus (D), stroke (S_2), vascular disease (V), age 65 to 74 years (A) and female gender (as a sex category [Sc]). The CHA_2DS_2-VASc score

Table 1. CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores.

Nomenclature		CHA_2DS_2-VASc-HS	CHA_2DS_2-VASc
C	Congestive heart failure	1	1
H	Hypertension	1	1
A_2	Age ≥75 years	2	2
D	Diabetes mellitus	1	1
S_2	History of stroke or TIA	2	2
V	Vascular disease	1	1
A	Age 65–74 years	1	1
Sc	Sex category (male gender)	1	1 (female gender)
H	Hyperlipidemia	1	–
S	Smoker	1	–
Total maximum		11	9

TIA — transient ischemic attack

was calculated by assigning 1 point for each of the presence of chronic heart failure, HT, DM, age 65–74 years, female gender and vascular disease and by assigning 2 points for history of stroke and age > 75 years. The CHA_2DS_2-VASc-HS score comprises hyperlipidemia (H) and smoking (S) in addition to the components of CHA_2DS_2-VASc score and male gender instead of female gender (Table 1). The maximum CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores were 9 and 11, respectively.

Statistical analyses

Statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS 20.0) for Windows (SPSS Inc., Chicago, Illinois, USA) and MedCalc 15 statistical software (Ostend, Belgium). Continuous data were presented as means and standard deviation. The Kolmogorov-Smirnov test was used to evaluate whether continuous variables were normally distributed. Differences in continuous variables between the two groups were determined by Student's t-test or Mann-Whitney U-test. Categorical variables were summarized as percentages and were compared by the χ^2 test or Fisher's exact test. The receiver operating characteristics (ROC) curve was also used to demonstrate the sensitivity and specificity of CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores and their cut-off values for predicting failed reperfusion. The area under curve (AUC) comparison of these scoring systems was performed using the Delong method [13]. A p value < 0.05 was considered statistically significant.

Results

The patients were divided into two groups according to the failure (n = 139) or success (n = 398) of thrombolysis. The mean age of patients was 59.9 ± 11.0 years and 82.7% of them were male (Table 2). The mean CHA_2DS_2-VASc score was significantly higher in failed reperfusion group than successful reperfusion group (2.1 ± 1.4 vs. 1.3 ± 1.2, respectively; p < 0.001). Similarly, the mean CHA_2DS_2-VASc-HS score was significantly higher in failed reperfusion group than successful reperfusion group (4.1 ± 1.7 vs. 2.6 ± ± 1.1, respectively; p < 0.001). For the prediction of failed reperfusion, the cut-off value of CHA_2DS_2--VASc score was ≥ 2 with a sensitivity of 80.90% and a specificity of 41.01% (AUC 0.660; 95% confidence interval [CI] 0.618–0.700; p < 0.001) and the cut-off value of CHA_2DS_2-VASc-HS score was ≥ 3 with a sensitivity of 76.1% and a specificity of 67.6% (AUC 0.764; 95% CI 0.725–0.799; p < 0.001) in the ROC curve analyses (Fig. 1). The AUC comparisons of CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scoring systems were performed based on failed reperfusion (Fig. 2). Pairwise comparisons of ROC curves were also performed and the results are demonstrated in Figure 2. Based on these results, the CHA_2DS_2-VASc-HS score was found to be better at a statistically significant level than CHA_2DS_2-VASc score to predict failed reperfusion in STEMI patients (p < 0.001). The baseline characteristics of both groups are summarized in Table 2. History of HT, DM, hyperlipidemia, heart failure, smoking, and CAD were significantly more

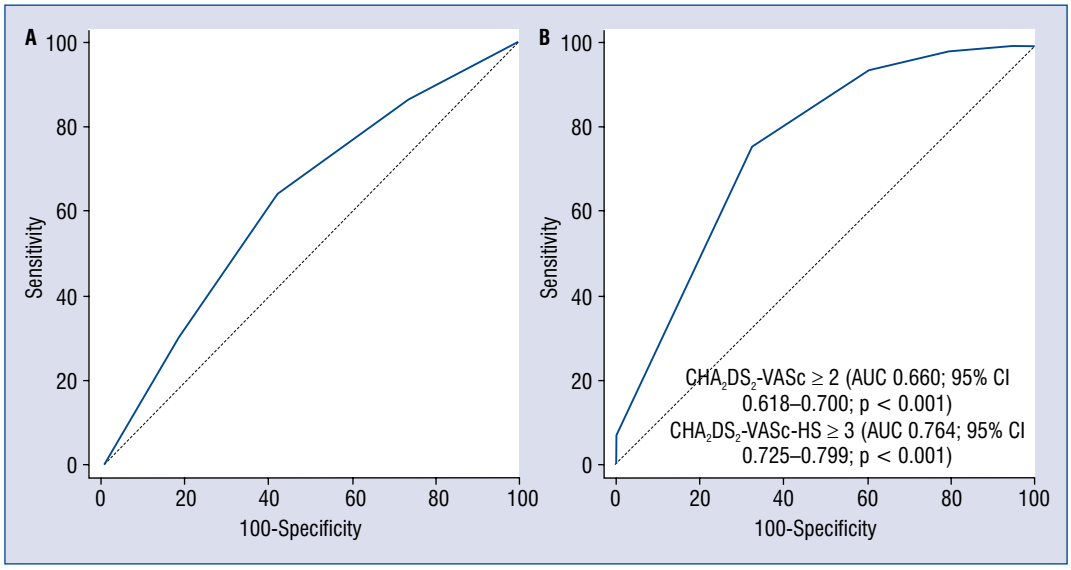

Figure 1. Receiver-operating characteristics analysis curves showing cutoff values for CHA_2DS_2VASc (**A**) and CHA_2DS_2-VASc-HS (**B**) scores for failed thrombolysis in patients with ST-segment elevation myocardial infarction (STEMI).

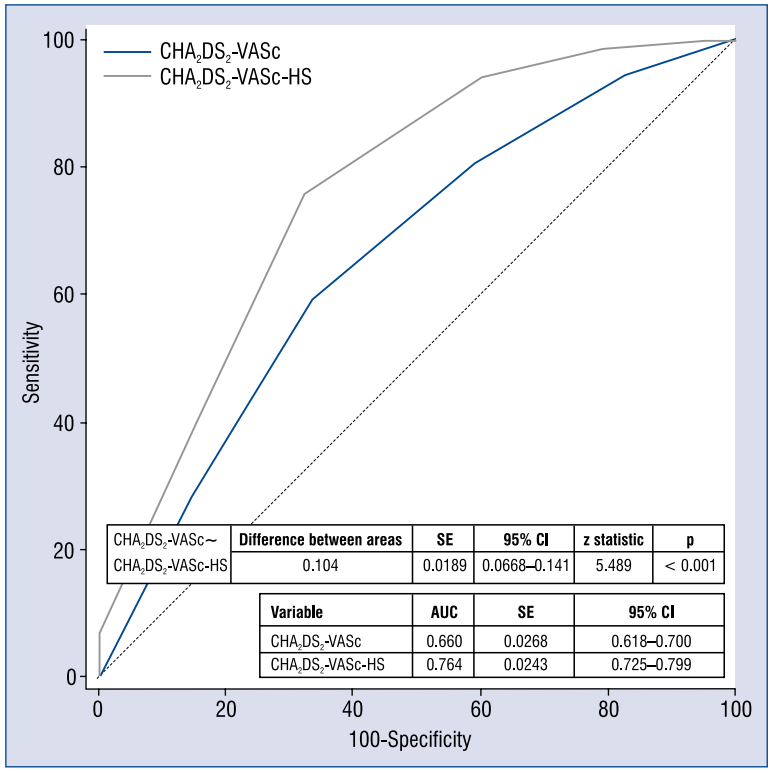

Figure 2. Comparison of receiver-operating characteristics analysis curves according failed reperfusion.

common in failed reperfusion group compared to the successful reperfusion group (for all; $p < 0.05$). There was no difference between two groups in terms of gender distribution, but the mean age of the patients in the failed reperfusion group was significantly higher than that of the successful reperfusion group (59.6 ± 12.3, 57.3 ± ± 10.5, respectively; $p = 0.032$). There were no statistically significant differences between two groups in levels of laboratory parameters such

Table 2. Baseline demographics and clinical characteristics.

Parameters	Successful thrombolysis (n = 398)	Failed thrombolysis (n = 139)	P
Age [year]	57.3 ± 10.5	59.6 ± 12.3	0.032
Male	327 (82.2%)	117 (84.2%)	0.935
Diabetes mellitus	92 (23.1%)	49 (35.3%)	0.005
Hypertension	162 (40.6%)	99 (71.2%)	< 0.001
Hyperlipidemia	77 (23.9%)	50 (35.9%)	< 0.001
Heart failure	25 (6.3%)	19 (13.7%)	0.006
Stroke	–	–	–
Smoking	234 (62.3%)	114 (82.0%)	< 0.001
Coronary artery disease	68 (17.1%)	41 (29.5%)	0.002
Coronary artery bypass grafting	21 (5.3%)	8 (5.8%)	0.830
Family history	99 (24.9%)	31 (22.3%)	0.533
Obesity	79 (24.5%)	32 (23.0%)	0.727
CHA_2DS_2-VASc	1.3 ± 1.2	2.1 ± 1.4	< 0.001
CHA_2DS_2-VASc-HS	2.6 ± 1.1	4.1 ± 1.7	< 0.001
Anterior myocardial infarction	125 (31.4%)	42 (30.2%)	0.794
Time from symptom onset to treatment [h]	2.1 ± 0.7	2.1 ± 0.8	0.596
Heart rate [bpm]	75.4 ± 16.8	74.4 ± 17.8	0.554
Systolic blood pressure [mmHg]	128 ± 30	137± 34	0.002
Diastolic blood pressure [mmHg]	76 ± 17	82 ± 19	0.001
Hemoglobin [g/dL]	14.4 ±2.8	14.6 ±2.6	0.792
Creatinine [mg/dL]	0.8 ± 0.1	0.8 ± 0.1	0.856
Total cholesterol [mg/dL]	184 ± 40	201± 51	< 0.001
Low density lipoprotein cholesterol [mg/dL]	108 ± 35	118 ± 45	0.009
High density lipoprotein cholesterol [mg/dL]	41 ± 11	43 ± 17	0.112
Triglycerides [mg/dL]	151 ± 91	146 ± 82	0.131

Data are shown as mean ± standard deviation or number (percentage).

as hemoglobin, creatinine, HDL-C and triglycerides. In contrast, total cholesterol and LDL-C levels were statistically and significantly higher in the failed reperfusion group than in the successful reperfusion group. Similarly, both systolic and diastolic blood pressure levels were statistically and significantly higher in failed reperfusion group than in the successful reperfusion group (Table 2).

Discussion

This study demonstrated that the CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores may be used as simple yet powerful tools to aid in prediction of failed reperfusion after thrombolytic therapy in STEMI patients. In addition, CHA_2DS_2-VASc-HS score was found to be of higher value in predicting failed reperfusion compared to the CHA_2DS_2-VASc score.

STEMI is a significantly worldwide cause of mortality and morbidity. While PCI is the golden standard for the treatment of STEMI patients, thrombolytic therapy is recommended in case a PCI cannot be performed by an experienced team within 90 min after first medical contact [11]. Delayed PCI was shown to be associated with poor clinical outcomes. While there is no clearly defined time for how long PCI can be delayed, it was shown that PCI can still be more beneficial than thrombolytic therapy in case of delays of up to 120 min [14, 15]. The most commonly used strategies to evaluate reperfusion after thrombolytic therapy include regression of ST segment resolution, complete recovery from pain or monitoring reperfusion arrhythmia. Still, all these parameters can be evaluated only after thrombolytic therapy.

Several studies previously investigated the potential predictors of failed reperfusion. Zairis et al. [4] showed that plasma level of CRP on admission

is a predictor of reperfusion failure after thrombolytic therapy in patients with STEMI. Baysal et al. [5] reported that there was a strong and independent association between increased red cell distribution width and failed thrombolysis in the setting of acute STEMI. Pereg et al. [6] reported in their study that a higher mean platelet volume correlated with failed thrombolysis in patients presenting with STEMI. In addition, Cetin et al. [7] demonstrated that an increased platelet distribution width was associated with failed reperfusion in STEMI patients. However, based on available research, there is currently no simple and practical scoring system that can be used to predict failed reperfusion. The CHA_2DS_2-VASc scores were initially developed for thromboembolism risk stratification in patients with AF [16]. Recent researches have extended the use of the CHA_2DS_2-VASc score to non-AF populations [9, 17–19].

There are some recently published studies investigating CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores in patients with acute coronary syndrome [17–20]. Bozbay et al. [20] showed that CHA_2DS_2--VASc score was a predictor of in-hospital and long-term adverse clinical outcomes in STEMI patients. Unal et al. [17] demonstrated that CHA_2DS_2-VASc score was an independent predictor of stent thrombosis. Moreover, in their study including patients who underwent coronary angiography for STEMI, Ipek et al. [19] found that CHA_2DS_2-VASc score was associated with a higher risk of no-reflow and in-hospital mortality rates in patients who underwent primary PCI due to STEMI. A study by Orvin et al. [21] reported that the CHA_2DS_2-VASc score predicted all-cause mortality and death or nonfatal myocardial infarction in a significant and linear manner. Cetin et al. [9] investigated patients who underwent diagnostic angiography and found that $CHADS_2$, CHA_2DS_2-VASc and CHA_2DS_2-VASc--HS scores were significantly correlated with the number of diseased coronary vessels and the Gensini score. In that study, they developed a new scoring system named CHA_2DS_2-VASc-HS, which incorporated hyperlipidemia and smoking, and replaced male with female gender in the CHA_2DS_2--VASc score [9]. Similarly, Tasolar et al. [18] found a positive correlation between CHA_2DS_2-VASc-HS score and the severity and complexity of CAD in patients with non-ST elevation acute coronary syndrome [18].

The present results underlined the significance of the CHA_2DS_2-VASc and especially CHA_2DS_2-VASc-HS scores as predictors of failed reperfusion after thrombolytic therapy in STEMI patients. But, this was the first study performed on STEMI patients who were given thrombolytic therapy.

In the present study, the significantly elevated CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores in patients in the failed reperfusion group can be explained by the association between these scores and the extent and severity of CAD. Moreover, in addition to predicting the severity and seriousness of CAD, higher scores also reflect increased thrombogenicity and thrombus load [22]. The findings of this study are important as they support the fact that increasing mean risk scores indicate a higher probability of failed reperfusion. The significance of both scores in predicting failed reperfusion is because their components, including HT, DM, old age and heart failure are also separately associated with CAD severity and poor outcomes in STEMI patients [9, 18, 19]. Moreover, incorporation of hyperlipidemia and smoking as risk factors for CAD into the newly developed CHA_2DS_2-VASc score further increased the predictive value for failed thrombosis. In the CHA_2DS_2-VASc-HS score, female gender in the CHA_2DS_2-VASc score is switched with male gender, which is a risk factor for CAD. However, due to the low proportion of female patients in this study, the potential impact of gender on failed reperfusion could not be demonstrated. Additional assessments should be performed in larger and distinct populations.

The CHA_2DS_2-VASc and CHA_2DS_2-VASc-HS scores represent simple, very useful and easy--to-remember bedside score for predicting failed reperfusion after thrombolysis in STEMI patients. It is believed herein, that these scores, especially CHA_2DS_2-VASc-HS, could be used in daily practice to estimate failed reperfusion risk for patients admitted to non-capable PCI hospitals. In addition, these simple scores can help physicians to determine transfer strategy for PCI-capable hospital such as ambulance or aircraft. If patients have a high risk of failed reperfusion, they may be referred by aircraft, rather than ambulance for faster transfer.

Limitation of the study

One of the major limitations of this study is that it was a single-center study. The absence of patients with a history of ischemic or hemorrhagic stroke also represents another major limitation. Nevertheless, stroke was not excluded from the scoring systems in order to guide future studies and avoid contravening the generic scoring systems.

Conclusions

Findings of the present study are important as they demonstrated that the simple and practical CHA_2DS_2-VASc and CHA_2DS_2VASc-HS scores can be useful in predicting failed reperfusion before thrombolytic therapy. In addition, these scores can help physicians who work in non-capable PCI hospitals to estimate risk of failed reperfusion.

Conflict of interest: None declared

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Predictive and protective role of high-density lipoprotein cholesterol in acute myocardial infarction

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Abstract

Background: *It is unclear whether high-density lipoprotein cholesterol (HDL-C) level predicts cardiovascular events and has a protective effect in patients with acute myocardial infarction (AMI) undergoing percutaneous coronary intervention (PCI) and statin treatment.*

Methods: *A total of 15,290 AMI patients receiving statins were selected from the Korean Myocardial Infarction Registry. Baseline HDL-C level was used to identify patients with low (group A), normal (group B), and high (group C) HDL-C levels according to the Adult Treatment Panel III criteria. Clinical outcomes were compared in propensity-adjusted and matched cohorts. The primary endpoint was a composite of cardiovascular death and recurrent myocardial infarction.*

Results: *At the median follow-up of 11.5 months, the primary endpoint occurred in 2.7% (112/4098), 1.4% (54/3910), and 1.2% (8/661) of patients in groups A, B, and C, respectively. In the propensity-adjusted cohort, low HDL-C level increased the risk of primary endpoint (hazard ratio [HR] 1.755, 95% confidence interval [CI] 1.274–2.417, p = 0.001), whereas high HDL-C level did not reduce this risk (HR 0.562, 95% CI 0.275–1.146, p = 0.113). In the propensity-matched cohort, low HDL-C level increased the risk of primary endpoint (HR 1.716, 95% CI 1.210–2.434, p = 0.002), whereas high HDL-C level reduced this risk (HR 0.449, 95% CI 0.214–0.946, p = 0.035).*

Conclusions: *In AMI patients treated with PCI and statins, low HDL-C level increases the risk of cardiovascular death and recurrent myocardial infarction, whereas high HDL-C level likely reduces the risk of cardiovascular events, especially for ST-elevation myocardial infarction.* (Cardiol J 2019; 26, 2: 176–185)

Key words: high-density lipoprotein cholesterol, acute myocardial infarction, cardiovascular events, statin

Introduction

Several randomized control trials have shown that persistent cardiovascular risk remains in spite of reducing the level of low-density lipoprotein cholesterol (LDL-C) with intensive statin therapy [1]. In contrast, an inverse relation between the level of high-density lipoprotein cholesterol (HDL-C) and the rate of cardiovascular events has been revealed in a number of studies [2, 3]. A high

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HDL-C level is associated with cardioprotective and anti-inflammatory effects, and achieving it represents a potential therapeutic strategy to reduce cardiovascular risk [4].

Whether low HDL-C levels predict poor cardiovascular outcomes in acute myocardial infarction (AMI) patients has been a matter of controversy [5, 6]. In this regard, vascular effects of HDL-C can be highly heterogeneous in various clinical conditions [7], and its anti-inflammatory function may be impaired in patients with coronary artery disease (CAD) [8]. It is therefore important to verify the protective role of high HDL-C levels in patients with AMI.

In the present study, the predictive and protective role of HDL-C in a cohort of Asian patients with AMI undergoing percutaneous coronary intervention (PCI) and intensive statin therapy were evaluated.

Methods

Study population

In this prospective, multicenter, observational registry-based study, the data of 31,149 patients with ST-elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) from 53 hospitals were retrieved from the Korean Acute Myocardial Infarction Registry (KAMIR) between 2006 and 2012 [9, 10]. This was retrospective study based on the KAMIR registry. The 53 participating centers included high-volume university or community hospitals with facilities for PCI and on-site cardiac surgery. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected by prior approval by the human research committee of each participating institution. Informed consent for use of data was obtained from each patient. Clinical and laboratory characteristics and outcomes were collected by trained study coordinators using a standardized case report form and protocol. Angiographic characteristics such as American College of Cardiology/American Heart Association (ACC/AHA) lesion type or thrombolysis in myocardial infarction (TIMI) flow grade were assessed by the surgeons. Clinical follow-up was performed at 1, 2, 6, 12, and 24 months after discharge from hospital.

The inclusion criteria for the present study were as follows: (1) age ≥ 18 years; (2) diagnosis of STEMI or NSTEMI; (3) absence of clinical events during hospitalization; and (4) statins use at discharge. The exclusion criterion was missing information on serum HDL-C level.

Among the 31,149 patients registered in the above mentioned database, a total of 15,290 AMI patients treated with statins were eligible for this study. The patients were divided into three groups based on serum HDL-C levels at baseline according to the Adult Treatment Panel III (ATP III) guidelines (group A: 7,308 patients with low HDL-C, group B: 6,827 patients with normal HDL-C, group C: 1,155 patients with high HDL-C) (Fig. 1). The median follow-up period was 347 days (interquartile range: 59–403 days). Follow-up information was obtained in 14,830 patients (97%, excluding 460 patients who died during hospitalization) among the initial 15,290 patients.

Definitions and outcomes

Blood samples were collected at admission, except for the samples used for obtaining lipid profiles, which were collected after overnight fasting.

According to the ATP III guidelines [11], a low HDL-C level (group A) was defined as a concentration of HDL-C below 40 mg/dL for men and 50 mg/dL for women. A high HDL-C level (group C) was defined as a concentration of HDL-C over 60 mg/dL. A normal HDL-C level (group B) was defined as an HDL-C concentration between the limits of the low and high HDL-C groups.

The primary outcome was the composite of cardiovascular death and recurrent MI during the follow-up period. Secondary outcomes included cardiovascular death, all-cause death, recurrent MI, any revascularization, and major adverse cardiac events (MACE), which included all-cause death, recurrent MI, and any revascularization during the follow-up. All events were identified by the patient's physician and confirmed by the principal investigator of each hospital.

Statistical analyses

Continuous variables were compared using Student's t-test or the Wilcoxon rank-sum test, and categorical variables were compared using the χ^2 test or Fisher's exact test, as appropriate. Because of significant differences in a large number of baseline clinical and angiographic characteristics between the three groups, propensity score adjustment was performed. Since only pairwise comparisons are allowed in propensity score adjustment, the groups were combined and compared in the following manner: low HDL-C group vs. combined normal-high HDL-C group and combined low-normal HDL-C group vs. high HDL-C group.

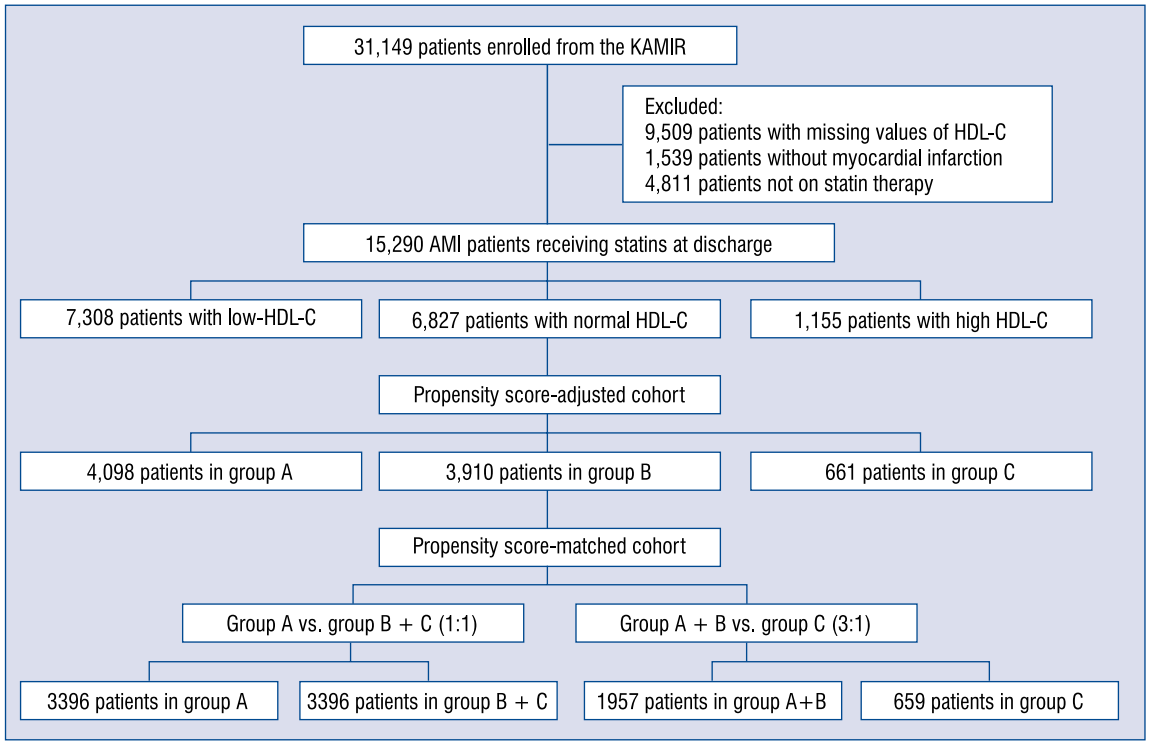

Figure 1. Study flowchart; AMI — acute myocardial infarction; HDL-C — high-density lipoprotein cholesterol; KAMIR — the Korean Acute Myocardial Infarction Registry.

In the main analysis, a propensity score was calculated and used to adjust the between-group comparisons of cardiovascular outcomes [12]. The propensity score was estimated using a non-parsimonious multivariate logistic regression model, with low HDL-C level or high HDL-C level in each subgroup as the dependent variable and characteristics that potentially affect cardiovascular outcomes, including age, sex, history of ischemic heart disease, hypertension, diabetes, dyslipidemia, smoking status, Killip class, number of diseased vessels, post-TIMI flow, initial left ventricular ejection fraction (LVEF), serum creatinine level, serum glucose level, peak troponin I, and use of acetylsalicylic acid, clopidogrel, beta-blockers, angiotensin converting enzyme inhibitors, aldosterone receptor blockers, spironolactone, and insulin.

An additional analysis was performed on matched pairs of patients between each subgroup (group A vs. group B + C, group A + B vs. group C). Each propensity score matching was performed using the nearest neighbor method (1:1 for group A vs. group B + C, 3:1 for group A + B vs. group C without replacement) with a caliper width of 0.1. Absolute standardized differences for all covariates before and after matching were estimated to evaluate bias reduction using the propensity score matching method. After propensity score matching, all absolute standardized differences were below 10%, indicating adequate matching. Comparisons of baseline clinical and angiographic characteristics between the matched groups were performed using Student's t-test for continuous variables and the χ^2 test for categorical variables.

Risk of negative cardiovascular outcomes between all the subgroups in the propensity score-adjusted cohort were compared using the Cox proportional hazard regression model with the propensity score as a covariate. Adjusted cumulative survival curves were calculated using the corrected group prognosis method. A secondary analysis was done using the Cox proportional hazard regression model stratified on the matched pairs. Proportional hazard assumptions were tested by using the log–log survival plot and Schoenfeld residuals. Subgroup analysis was also performed only in the propensity score-matched cohort based on the type of MI (STEMI or NSTEMI).

Sensitivity analysis was performed to assess the robustness of results. An inverse probability of treatment weight (IPTW) approach was used because it utilizes the whole patient population rather than the reduced population obtained by the propensity score matching, resulting in greater power and precision [13].

A multiple Cox regression analysis was performed to predict risk factors of negative cardiovascular outcome during the follow-up using baseline and angiographic characteristics associated with cardiac death and MI in a simple Cox regression analysis ($p < 0.1$) with > 90% data availability.

All reported p values were 2-sided, and p values < 0.05 were considered to indicate statistically significant differences. All analyses were performed with SPSS 21.0 for Windows (SPSS Inc., Chicago, IL) and R (version 2.14.2) using freely distributed statistical packages, as well as SAS software, version 9.3 (SAS Institute, Cary, NC, USA).

Results

Major differences in baseline and angiographic characteristics between the three groups were consistently found in propensity score-adjusted cohort (Table 1). After matching between divided subgroups, all absolute standardized differences were within 10%, which suggests adequate matching.

Overall study outcomes

In the propensity score-adjusted cohort, 174 (2%) patients experienced at least one primary event (cardiovascular death or recurrent MI) during the follow-up period. The rate of primary outcome was highest in low HDL-C group (group A) and similar in normal and high HDL-C groups (groups B and C) (Fig. 2). An increased risk of primary outcome (hazard ratio [HR] 1.755, confidence interval [CI] 1.274–2.417, $p = 0.001$) was found in group A, which was driven by an increase in cardiovascular death (HR 2.233, CI 1.465–3.404, $p < 0.001$) and eventually in all-cause death (HR 1.486, CI 1.084–2.036, $p = 0.014$), whereas the risk of primary outcome was not reduced in group C (HR 0.562, CI 0.275–1.146, $p = 0.113$) (Table 2). There were no differences in the risk of MI recurrence and MACE.

Outcomes in patients with low HDL-C level

When these analyses were repeated in the matched cohort (group A vs. group B + C), risk of primary outcome was increased in Group A (2.5% vs. 1.5%, HR 1.716, CI 1.210–2.434, $p = 0.002$) (Fig. 3A, Table 3). There were no differences in the risks of MI recurrence, all-cause death, and MACE between the groups.

Analyses by the propensity score matching method were repeated in the subgroups including STEMI and NSTEMI patients. In the matched cohort (group A vs. group B + C), low HDL-C level tended to be associated with an increased risk of primary outcome in STEMI patients, but the difference was not statistically significant (HR 1.542, CI 0.969–2.453, $p = 0.068$). In contrast, low HDL-C level was associated with an increased risk of primary outcome in NSTEMI patients (HR 2.058, CI 1.195–3.546, $p = 0.009$).

Outcomes in patients with high HDL-C level

The analysis of the second matched cohort (group A + B vs. group C) revealed a decrease in risk of primary outcome (2.7% vs. 1.2%, HR 0.449, CI 0.214–0.946, $p = 0.035$) (Fig. 3B, Table 3). There were no differences in the risk of secondary outcomes. The analyses by the propensity score matching method were repeated in STEMI and NSTEMI subgroups. Interestingly, high HDL-C level was associated with a reduction in the risk of primary outcome in the STEMI patients (HR 0.267, CI 0.081–0.873, $p = 0.029$) but not in the NSTEMI patients (HR 0.774, CI 0.292–2.053, $p = 0.606$).

Sensitivity analysis

Sensitivity analyses were performed for the primary outcome using weighted Cox regression by the IPTW method. An increased risk of cardiovascular death and MI was found in the low HDL-C group (HR 1.758, 95% CI 1.414–2.186, $p < 0.001$). Furthermore, the risk of cardiovascular death and MI was reduced in the high HDL-C group (HR 0.632, 95% CI 0.500–0.797, $p < 0.001$). This confirmed the results of the main analyses.

Independent predictors of cardiovascular events

The simple Cox regression analysis of the propensity score-adjusted cohort showed that old age, female sex, high Killip class, history of prior ischemic heart disease, hypertension, diabetes mellitus, three-vessel disease, post-procedural TIMI flow grades 2 and 3, low LVEF, high serum levels of glucose or creatinine at presentation, and high peak serum level of troponin were associated with cardiovascular death and MI during the follow-up (Table 4). After the adjustment for old age, high Killip class, and low LVEF continued to show a significant association with cardiovascular death and MI during the follow-up.

Discussion

In the present study, the predictive and protective role of HDL-C in AMI patients was inves-

Table 1. Baseline clinical and procedural characteristics.

	Group A	Group B	Group C	P
	Low HDL-C (n = 4,098)	Normal HDL-C (n = 3,910)	High HDL-C (n = 661)	
Age [years]	62.2 ± 12.6	63.1 ± 12.6	64.3 ± 12.2	< 0.001
Male sex	5972 (78%)	7606 (70%)	590 (62.6%)	< 0.001
Ischemic heart disease	1181 (15.5%)	1525 (14.1%)	232 (14.8%)	0.028
Diabetes mellitus	2418 (32.1%)	2651 (24.7%)	317 (20.2%)	< 0.001
Hypertension	3804 (50.3%)	5321 (49.5%)	753 (48.1%)	0.251
Dyslipidemia	956 (13.6%)	1297 (13.0%)	157 (10.8%)	0.014
Smoking	3735 (49.4%)	4597 (42.7%)	578 (37.1%)	< 0.001
Family history of ischemic heart disease	659 (9.3%)	889 (8.9%)	113 (7.8%)	0.178
Systolic BP at presentation [mmHg]	127 ± 30	130 ± 27	133 ± 27	< 0.001
Diastolic BP at presentation [mmHg]	78 ± 27	79 ± 17	81 ± 16	< 0.001
Killip class:				
I	5412 (75.1%)	7844(76.3%)	1056 (70.7%)	< 0.001
II	910 (12.6%)	1346 (13.1%)	242 (16.2%)	
III	565 (7.8%)	752 (7.3%)	142 (9.5%)	
IV	320 (4.4%)	336 (3.3%)	53 (3.5%)	
Door-to-balloon time [min]	173 ± 196	176 ± 199	179 ± 208	0.576
Left ventricular ejection fraction [%]	52.4 ± 11.6	52.5 ± 13.1	52.2 ± 15.6	0.538
Peak troponin I [ng/mL]	39.9 ± 88.2	44.2 ± 116.5	49.6 ± 255.5	0.015
Serum creatinine [mg/dL]	1.25 ± 1.54	1.10 ± 1.4	1.05 ± 1.07	< 0.001
Serum glucose [mg/dL]	171.6 ± 82.4	165.3 ± 74.5	164.9 ± 74.4	< 0.001
Total cholesterol [mg/dL]	172 ± 44	189 ± 42	201 ± 45	< 0.001
HDL-C [mg/dL]	33 ± 5	47 ± 5	70 ± 13	< 0.001
LDL-C [mg/dL]	110 ± 37	120 ± 41	117 ± 42	< 0.001
Triglycerides [mg/dL]	150 ± 116	120 ± 93	102 ± 88	< 0.001
C-reactive protein [mg/dL]	11.00 ± 56.48	9.13 ± 52.90	8.30 ± 53.99	0.059
Medications at discharge:				
Acetylsalicylic acid	7520 (98.2%)	10661 (98.1%)	1543 (97.7%)	0.312
Clopidogrel	7269 (94.9%)	10241 (94.3%)	1455 (92.3%)	< 0.001
Calcium channel blockers	734 (9.8%)	1075 (10.1%)	171 (11.1%)	0.3
Beta-adrenergic blockers	6061 (79.5%)	8534 (78.8%)	1217 (77.4%)	0.148
ACE inhibitors	4710 (62%)	6972 (64.8%)	1032 (65.9%)	< 0.001
Angiotensin receptor blockers	1652 (22%)	2228 (20.8%)	291 (18.8%)	0.011
Spironolactone	621 (8.3%)	901 (8.5%)	120 (7.8%)	0.645
Insulin	127 (1.7%)	152 (1.4%)	12 (0.8%)	0.02
Oral hypoglycemic agents	1201 (15.7%)	1499 (13.8%)	214 (13.5%)	0.001
Number of diseased vessels:				< 0.001
1	2861 (40.4%)	4588 (46%)	701 (51.4%)	
2	2180 (30.8%)	2966 (29.7%)	402 (29.5%)	
3	1808 (25.5%)	2140 (21.4%)	232 (17%)	
Left main disease	229 (3.2%)	288 (2.9%)	30 (2.2%)	
Culprit lesion:				< 0.001
Left anterior descending	3022 (42.9%)	4952 (49.8%)	747 (54.9%)	
Left circumflex	1238 (17.6%)	1712 (17.2%)	228 (16.8%)	
Right coronary artery	2646 (37.6%)	3111 (31.3%)	360 (26.5%)	
Left main tract	134 (1.9%)	170 (1.7%)	26 (1.9%)	
Successful PCI	6466 (97.6%)	9161 (97.5%)	1226 (96.8%)	0.403
Post-procedural TIMI flow grade:				0.125
0	112 (1.7%)	116 (1.3%)	23 (1.8%)	
1	61 (0.9%)	79 (0.9%)	13 (1%)	
2	229 (3.6%)	354 (3.9%)	56 (4.5%)	
3	6023 (93.7%)	8542 (94%)	1155 (92.6%)	

ACE — angiotensin converting enzyme; BP — blood pressure; HDL-C — high-density lipoprotein cholesterol; LDL-C — low-density lipoprotein cholesterol; PCI — percutaneous coronary intervention; TIMI — thrombolysis in myocardial infarction

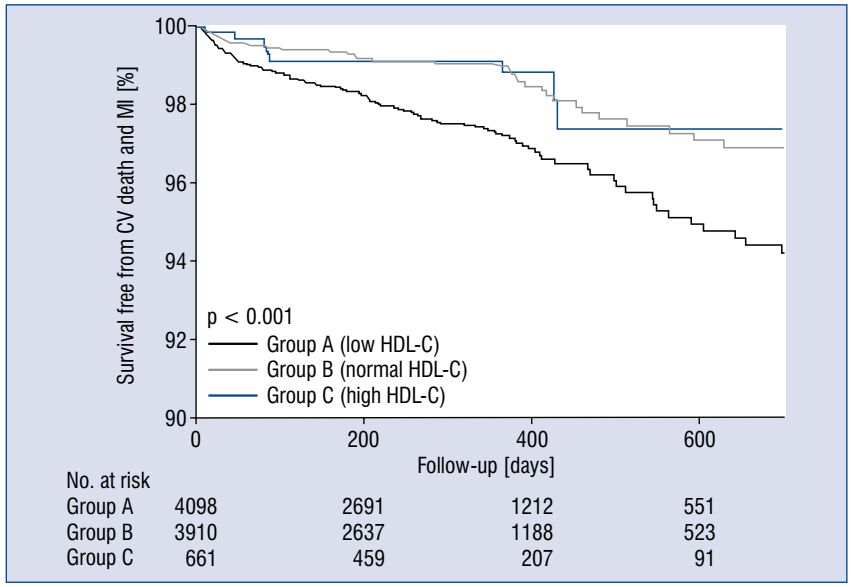

Figure 2. Survival curves free from cardiovascular (CV) death and myocardial infarction (MI) during follow-up in the propensity score-adjusted cohort; HDL-C — high-density lipoprotein cholesterol.

Table 2. The risk of negative clinical outcomes for patients with low and high high-density lipoprotein cholesterol (HDL-C) level in the propensity-adjusted cohort.

	Low HDL-C		High HDL-C	
	HR (95% CI)	P	HR (95% CI)	P
Cardiovascular death and MI	1.755 (1.274-2.417)	0.001	0.562 (0.275-1.146)	0.113
Cardiovascular death	2.233 (1.465-3.404)	< 0.001	0.775 (0.359-1.675)	0.517
Recurrent MI	1.203 (0.725-1.996)	0.474	0.192 (0.027-1.389)	0.102
All-cause death	1.486 (1.084-2.036)	0.014	0.964 (0.556-1.673)	0.897
MACE	1.022 (0.877-1.190)	0.65	0.915 (0.697-1.202)	0.524

CI — confidence interval; HR — hazard ratio; MI — myocardial infarction; MACE — major adverse cardiac event

tigated. evidence was found that the initial level of HDL-C affected cardiovascular outcomes in a cohort of Asian patients with acute AMI that were treated with statins. Thus, the rate of cardiovascular death and MI recurrence was higher in the patients with low HDL-C level, whereas high HDL-C level was associated with a lower rate of major cardiovascular events. Importantly, the application of different adjustment methods did not affect these findings. Moreover, subgroup analyses revealed that low HDL-C level was associated with a significantly higher risk of major cardiovascular events in the NSTEMI patients and only a modestly increased risk in the STEMI patients. Finally, high HDL-C level was associated with a lower risk of major cardiovascular events only in STEMI patients.

Lower HDL-C levels have been shown to be associated with a higher risk of cardiovascular events and greater severity of atherosclerosis even in patients with lower LDL levels, including those treated with statins [2]. Moreover, several studies have demonstrated that low HDL-C level in NSTEMI patients was predictive of major adverse cardiovascular events [5, 14]. In addition, low initial HDL-C level was associated with a significantly higher risk of cardiovascular events in STEMI patients [15]. However, the design of the above studies included the use of a constant value of HDL-C, and baseline and angiographic characteristics that might affect clinical outcomes were not properly compensated for. In order to rule out confounding effects of covariates, a propensity score model was built and two 1:1 cohorts of

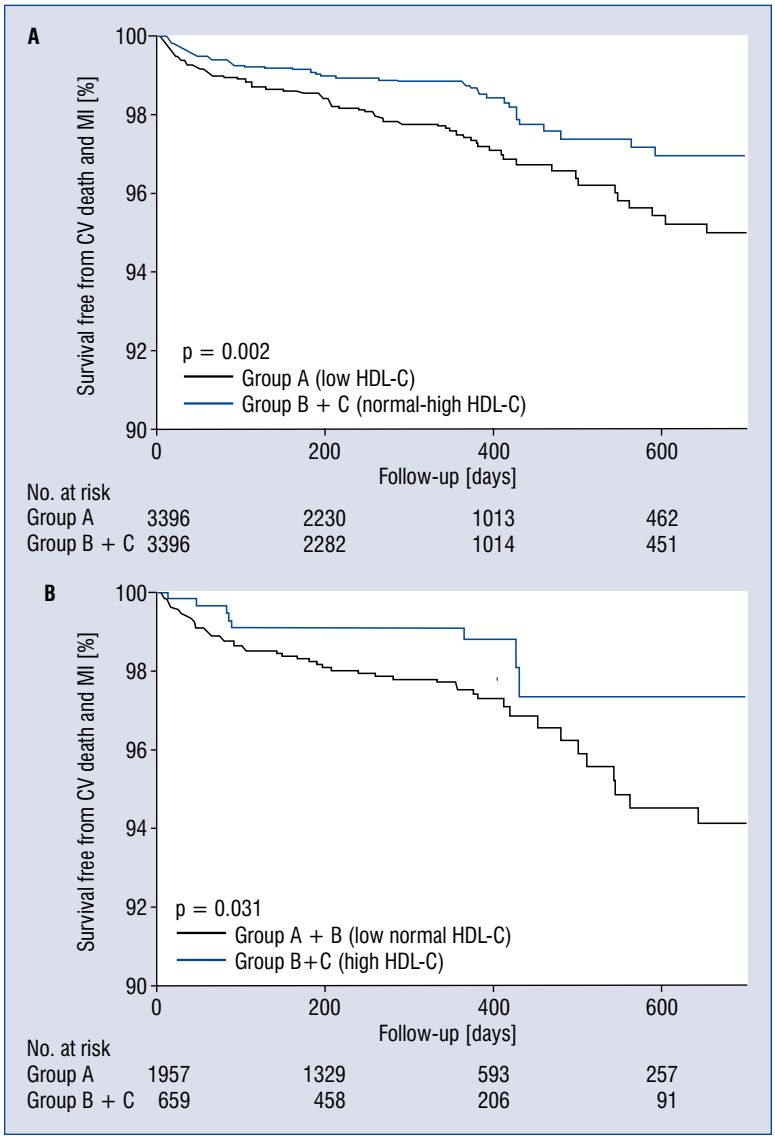

Figure 3. Survival curves free from cardiovascular death and myocardial infarction during follow-up in Group A vs. Group B+C (**A**) and Group A+B vs. Group C (**B**) in the propensity score-matched cohort; CV — cardiovascular; HDL-C — high-density lipoprotein cholesterol; MI — myocardial infarction.

optimally matched patients were obtained in the present study. Low initial HDL-C level was found to directly correlate with cardiovascular events (HR 1.716). Moreover, a consistent result (HR 1.758) was obtained using IPTW methods. The present analysis strengthens the notion that low HDL-C levels may be a predictor of cardiovascular outcomes in AMI patients.

The vasoprotective effect of HDL-C is thought to be related to reverse macrophage cholesterol transport [16]. Furthermore, it has been recently found that HDL-C facilitates endothelial homeostasis via the increase in nitric oxide production as well as the inhibition of critical pathways involved in vascular inflammation and endothelial apoptosis. It has also been reported that the ability of HDL-C to stimulate nitrate oxide production and promote endothelial repair is impaired in patients with CAD [17]. Based on these observations, the term "dysfunctional HDL-C" was introduced, which indicates the loss of anti-inflammatory and vasoprotective effects [8]. The results of a recent study that used the values of > 50 mg/dL for women and > 40 mg/dL for men, as a definition of high HDL-C level have suggested that higher HDL-C levels are not associated with reduced risk of vascular events in CAD patients [18]. In the present study, high HDL-C level as > 60 mg/dL were defined accord-

Table 3. The incidence and risk of negative clinical outcomes in patients with low and high high-density lipoprotein cholesterol (LDL-C and HDL-C) level in the propensity-matched cohort.

Low HDL-C	Group A (n = 3,396)	Group B + C (n = 3,396)	HR (95% CI)	P
Cardiovascular death and MI	85 (2.5%)	50 (1.5%)	1.716 (1.210–2.434)	0.002
Cardiovascular death	57 (1.7%)	29 (0.9%)	1.981 (1.267–3.099)	0.003
Recurrent MI	28 (0.8%)	21 (0.6%)	1.348 (0.765–2.377)	0.301
All-cause death	78 (2.3%)	58 (1.7%)	1.365 (0.972–1.918)	0.073
MACE	287 (8.5%)	284 (8.4%)	1.007 (0.855–1.187)	0.931
High HDL-C	**Group A + B (n = 1,957)**	**Group C (n = 651)**	**HR (95% CI)**	**P**
Cardiovascular death and MI	52 (2.7%)	8 (1.2%)	0.449 (0.214–0.946)	0.035
Cardiovascular death	34 (1.7%)	7 (1.1%)	0.604 (0.268–1.363)	0.225
Recurrent MI	18 (0.9%)	1 (0.2%)	0.161 (0.021–1.203)	0.075
All-cause death	50 (2.6%)	14 (2.1%)	0.824 (0.456–1.491)	0.523
MACE	162 (8.3%)	57 (8.6%)	1.028 (0.760–1.391)	0.856

CI — confidence interval; HR — hazard ratio; MI — myocardial infarction; MACE — major adverse cardiac event

Table 4. Independent predictors of cardiovascular death and myocardial infarction.

Variable	Simple Cox regression		Multiple Cox regression	
	HR (95% CI)	P	HR (95% CI)	P
Age (1-year increase)	1.042 (1.029–1.056)	< 0.001	1.035 (1.020–1.051)	< 0.001
Female sex	1.716 (1.265–2.327)	< 0.001		
Killip class 3/4	3.281 (2.329–4.621)	< 0.001	1.616 (1.106–2.359)	0.001
Ischemic heart disease	1.588(1.088–2.318)	0.016		
Hypertension	1.411 (1.046–1.903)	0.024		
Diabetes mellitus	1.570 (1.150–2.143)	0.004		
Dyslipidemia	1.058 (0.692–1.618)	0.793		
Current smoking	0.768 (0.566–1.042)	0.089		
Post-procedural TIMI flow grade 2–3	0.766 (0.284–2.066)	0.598		
Three-vessel disease	1.980 (1.458–2.688)	< 0.001		
Low LVEF	0.947 (0.936–0.959)	< 0.001	0.962 (0.948–0.975)	< 0.001
Serum glucose level	1.002 (1.001–1.004))	0.002		
Serum creatinine level	1.130 (1.048–1.219)	0.001		
Serum peak troponin level	1.001 (1.000–1.001)	0.043		

CI — confidence interval; HR — hazard ratio; LVEF — left ventricular ejection fraction; TIMI — thrombolysis in myocardial infarction

ing to ATP III guidelines. According to results of the propensity-based analysis, high HDL-C level was associated with reduced risk of cardiovascular events (HR 0.449) in AMI patients. This finding was confirmed by the use of IPTW methods (HR 0.632). Therefore, this analysis suggests that high initial HDL-C level might protect against cardiovascular events in AMI patients.

Several clinical trials and meta-analyses indicated that raising HDL-C might reduce future cardiovascular events and also the atherosclerotic burden itself. Several studies which were conducted based on the modulation of HDL-C by agonizing nuclear transcription factors and the enzyme responsible for HDL metabolism in serum have failed to demonstrate the protection against future cardiac

events [19]. HDL metabolism and modulation were far more complex than was thought, and changes in specific circumstances such as disease entity and disease progression [20]. Focus now moved to modulating various sub-fraction of HDL-C, which might lead to reduced residual risk after statin therapy [21].

Limitations of the study

The main limitation of the present study is its retrospective nature. Despite the use of propensity score analysis and sensitivity analysis that employed the IPTW approach to control for selection bias, unidentified confounders may have influenced the results. Furthermore, several studies have suggested that serum lipid levels after AMI may not represent true baseline levels [22], which may potentially have affected results. However, other reports indicate that HDL-C levels obtained within the first 24 to 48 hours subsequent tohospital admission are a reliable measure of true baseline status [23, 24], which justifiesthis approach to the HDL-C level measurements. Finally, lipid profile was not monitored during the follow-up period.

Conclusions

Initial HDL-C levels may predict cardiovascular events in AMI patients undergoing intensive statin treatment. In particular, low HDL-C levels were associated with increased incidence of cardiovascular death and recurrent MI. Furthermore, high HDL-C levels were possibly associated with reduced risk of cardiovascular events, especially in STEMI patients, indicating a potential protective effect.

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Conflict of interest: None declared

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Low CPNE3 expression is associated with risk of acute myocardial infarction: A feasible genetic marker of acute myocardial infarction in patients with stable coronary artery disease

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Abstract

Background: *Gene COPINE III may be related to a phosphoprotein with intrinsic kinase activity and belongs to an unconventional kinase family. The CPNE3 gene may be used as a biomarker for assessment of occurrence and prognosis of various tumors.*

Methods: *Peripheral blood was collected from 87 stable coronary artery disease (CAD) patients and 91 acute myocardial infarction (AMI) patients. Real-time quantitative polymerase chain reaction test and the western blot method were adopted to measure expression quantity of CPNE3 gene at the mRNA level and the protein level.*

Results: *The expression of the CPNE3 gene in peripheral blood of AMI patients was significantly lower than those in peripheral blood of stable CAD patients. Low expression of CPNE3 gene was found to be unrelated to level of fasting blood glucose and serum blood lipid of patients, quantity of cardiac troponin and time of onset but was found to be correlated to the Gensini score for coronary artery. When the expression of CPNE3 gene at the mRNA level in peripheral blood was used as the criterion for diagnosing AMI, its sensitivity, specificity, positive predictive value and negative predictive value were 69%, 64.8%, 68.6% and 65.2%, respectively.*

Conclusions: *Compared to stable CAD patients, AMI patients have a lower expression of CPNE3 gene in their peripheral blood. Patients who have low CPNE3 expression in peripheral blood are more likely to suffer from AMI than those with stable CAD. Low expression of CPNE3 gene serves as an potential independent risk factor of AMI.* (Cardiol J 2019; 26, 2: 186–193)

Key words: CPNE3 gene, acute myocardial infarction, stable coronary artery disease, independent risk, peripheral blood, genetic marker

Introduction

In the United States, 40% of all cases of death every year are related to coronary artery disease (CAD) and it is estimated that such disease will be a major cause of death around the world in the next decades [1]. In particular, there is a potential and fatal risk of acute myocardial infarction (AMI) in the progression of CAD [2, 3]. In patients with CAD, conventional risk factors were present at a much higher prevalence than commonly believed, with 15% to 20% of patients lacking any of the conventional risk factors for the disease [4]. Just like other chronic diseases, CAD is a complex polygenic disease, based on the incidence rate of AMI which increases with age, which is jointly caused by genetic factors and environmental factors [5].

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According to various literature, gene expression level in peripheral blood can reflect changes of various complex diseases including cardiovascular disease and serves as an extremely significant biomarker for detection and verification of diseases [6, 7]. For example, serving as a potential inflammation marker, an increase in expression of α-defensin in peripheral blood may serve to predict the risk of CAD occurrence among hyperlipidemia patients [8].

Gene COPINE III may be related to a phosphoprotein with intrinsic kinase activity and belongs to an unconventional kinase family [9]. It may have an influence on membrane protein, lipid and other activities [10]. CPNE3 gene can be used to predict metastatic potential of small cell lung cancer and serves as an index for prognosis of patients or a therapeutic target [11]. Moreover, the CPNE3 gene also plays a role with high correlation in carcinogenesis of prostate cancer [12]. It has also been proved that CPNE3 gene is correlated to schizophrenia [13].

The result of a previous analysis on profile of differential gene expression (2 pools, 3 subjects in each pool) in peripheral blood for AMI conducted by this research team indicates that AMI patients have a lower expression in their peripheral blood than stable CAD patients, for which the time of expression is 0.484 time. Therefore, by using the method of expanding the sample size of clinical data, this research aims to verify the relationship of CPNE3 gene AMI.

Methods

Subjects

Among patients admitted into Department of Cardiovascular Medicine, China-Japan Union Hospital of Jilin University from April 2016 to September 2016 and subject to coronary angiography, 91 patients definitively diagnosed with AMI according to the global uniform definition of myocardial infarction issued in 2012 [14] were selected to form the AMI group and 87 patients diagnosed with stable CAD [15] based on 2013 European Society of Cardiology guidelines were selected to form the control group (1. Narrowing of ≥ 50% in the left main coronary artery and ≥ 70% in one or several of the major coronary arteries. 2. The duration of discomfort is brief — no more than 10 min in the majority of cases and more commonly even several minutes or less).

Statement of ethical approval

The Ethics Committee, China-Japan Union Hospital of Jilin University approved this research. Collection of samples and information about all subjects was approved by the subjects, from whom informed consent forms were signed.

Table 1. Sequence of RT-PCR primers.

Genes		Genes primer sequence (5′–3′)
CPNE3	F[a]	GTCAGACCCTTTATGTGTGTTGT
	R[b]	TGGAAAATTGGGGATTCAAGCAA
GAPDH	F[a]	ACGGATTTGGTCGTATTGGGCG
	R[b]	CTCCTGGAAGATGGTGATGG

F[a] — sequence from sense strands; R[b] — sequence from anti-sense strands

Peripheral blood collection, total RNA extraction and cDNA synthesis

The collection of 4 mL of peripheral venous blood of each subject and conducting total RNA extraction from the collected peripheral blood by using total RNA extraction reagent kit was carried out (RNAsimple Total RNA Kit, Tiangen Biotech (Beijing) Co. Ltd. Beijing) according to instructions on the reagent kit. Reverse transcription of 1 μg of the qualified total RNA was conducted by using reverse transcription reagent kit (TOYOBO Rever Tra Ace qPRC RT kit, Shanghai) and the obtained cDNA sample was stored under conditions with a temperature of -20°C for real-time (RT) quantitative polymerase chain reaction (PCR) in the next step.

Real-time quantitative PCR test

Polymerase chain reaction amplification was conducted with SYBR real-time quantitative PCR reagent kit (SYBR Premix Ex Taq TM, TaKaRa, Dalian). The 20 μL-reaction system was adopted, for which each reaction included: 10 μL of SYBR Premix Ex Taq TM, 0.5 μL of forward primer and 0.5 μL of reverse primer (concentration should be 10 μmol/L), 8 μL of nuclease-free double distilled water and 1 μL of cDNA template. Amplification was realized by using Mx3005P RT quantitative PCR system (Strata Gene). Relative expression quantity $2^{-\Delta Ct}$ (ΔCt = Target Gene Ct Value — Reference Gene Ct Value) was used to express the obtained cycle thresholds (Ct) of each sample and a comparison was conducted [16]. Design of PCR primer was conducted according to CPNE3 gene sequence provided by NCBI Database and synthesis was completed by Shanghai-based Sangon Biotech. Primer sequence is indicated in Table 1.

Table 2. Comparison of clinical data between the acute myocardial infarction (AMI) group and the stable coronary artery disease (CAD) group.

Categories of data	The AMI group (n = 91)	The stable CAD group (n = 87)	$t/\chi^2/z$	P
Age [years]	64.55 ± 11.464	61.32 ± 8.452	2.063	0.041
Sex:			0.186	0.666
Male	60 (65.9)	69 (69.0)		
Female	31 (34.1)	27 (31.0)		
BMI [kg/m²]	24.802 (22.477–27.357)	25.799 ± 3.209	–1.711	0.087
Hypertension	44 (48.4)	45 (51.7)	0.202	0.653
Family medical history	7 (7.7)	4 (4.6)	0.718	0.397
Systolic pressure [mmHg]	133.73 ± 23.488	136.04 ± 20.524	–0.350	0.727
Diastolic pressure [mmHg]	81 (75.75–91)	80.84 ± 12.61	–1.136	0.256
Smoking history	41 (45.1)	40 (46.0)	0.015	0.902
Diabetes	20 (22.0)	28 (32.2)	2.352	0.125
Fasting blood-glucose [mmol/L]	6.03 (5.085–8.235)	5.81 (5.240–8.170)	–0.360	0.719
Total cholesterol [mmol/L]	4.553 ± 1.358	4.334 ± 1.010	1.194	0.234
Triglyceride [mmol/L]	1.57 (1.160-2.303)	1.74 (1.140–2.500)	–0.500	0.617
LDL-C [mmol/L)	3.091 ± 1.101	2.855 ± 0.844	1.569	0.118
HDL-C [mmol/L]	0.94 (0.805–1.133)	0.88 (0.770–1.070)	–0.896	0.370
Ejection fraction [%]	63 (42–65)	65 (63–67.5)	–3.530	0.000

BMI — body mass index; HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol

Statistical analysis

All data were statistically analyzed with SPSS24.0 software. When the measured data conformed to normal distribution, statistical description was conducted by using $\overline{X} \pm S$ and inter-group difference comparison was realized through using independent T test analysis. When measurement data did not conform to normal distribution, median and inter-quartile range was adopted to conduct statistical description and inter-group difference comparison was realized with rank-sum test. Statistical description of enumeration data was realized through the use of frequency number and χ^2 test to analyze inter-group differences. Binary logistic regression analysis was conducted to analyze relevant risk factors of AMI. As for the correlation between relative expression quantity of CPNE3 gene, cardiac troponin I and Gensini score, double-variable correlation analysis was conducted to analyze any correlation. Statistical result characterized by $p < 0.05$, bilaterally, was deemed as having statistical significance.

Results

Clinical data analysis

It is indicated by the results of clinical data analysis on the subjects that: There is no significant statistical difference between the two groups in the following aspects: Age, sex, body mass index, history of hypertension, family history of coronary heart disease, systolic pressure, triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C). Those patients in the AMI group are older than patients in the stable CAD group and such difference is statistically significant ($t = 2.063$, $p = 0.041$). It was also found that left ventricular ejection fraction (EF) was significantly different between the two groups ($Z = –3.530$, $p = 0.000$; see Table 2 for details).

Comparative analysis on relative expression quantity of CPNE3 gene at the mRNA level between the AMI group and the stable CAD group

ΔCt value of each sample obtained through RT-PCR was the mean value obtained through three repeated measurements on each sample. The results indicate that $2^{-\Delta Ct}$ of the AMI group is 0.020 (0.016–0.032) and $2^{\Delta\Delta Ct}$ of the stable CAD group was 0.029 (0.021–0.067), for which there is a significant statistical difference ($Z = –4.231$, $p = 0.000$) between these two groups. The relative expression quantity of CPNE3 gene at the mRNA level in peripheral blood of patients in the AMI

group was significantly lower than that of patients in the stable CAD group, for which the relative expression quantity of CPNE3 gene of the AMI group is 0.69 times that of the stable CAD group (see Figure 1 for details).

Analysis on the result of expression of CPNE3 gene at the protein level in peripheral blood

Western blot was conducted on peripheral blood of patients with β-actin as the reference. The results indicated that the relative expression of CPNE3 was 0.925 ± 0.118 in the AMI group and 2.599 ± 0.261 in the stable CAD group. Compared to stable CAD patients, AMI patients have a low expression of CPNE3 at the protein level in their peripheral blood and the expression of CPNE3 of the AMI group at the protein level is 0.356 times that of the stable CAD group (see Figure 2 for details).

Analysis on correlation between expression quantity of CPNE3 gene and age, serum blood lipid and blood glucose, ejection fraction of patients

Based on stratification standard for blood lipid level [17], all subjects included were divided into groups: with normal TC (< 5.18 mmol/L), with increased TC (≥ 5.18 mmol/L), with normal TG (< 1.76 mmol/L) with increased TG (≥ 1.76 mmol/L), with normal LDL-C (< 3.37 mmol/L) with increased LDL-C (≥ 3.37 mmol/L),with normal HDL-C (≥ 0.907 mmol/L) and the group with decreased HDL-C (< 0.907 mmol/L). Based on the standard level of fasting blood glucose [18], all subjects were divided into groups with normal level of fasting blood glucose (≤ 6.0) and a group with an increased level of fasting blood glucose (> 6.0). Based on standard age groups of Chinese people, all subjects were divided into groups at an advanced age (> 65) and at a younger age (≤ 65). All the subjects were divided into groups with normal EF (≥ 50%) and with low EF (< 50%). The result indicates that there is a difference ($p = 0.008$) in the expression quantity of the CPNE3 gene at the mRNA level between the group at an advanced age and the group at a younger age (see Table 3 for detail of the results).

Analysis on correlation between expression quantity of CPNE3 gene at mRNA level and age of patient and AMI using logistic regression analysis

Based on the cut-off value of relative expression quantity of CPNE3 gene, all the subjects were divided into a group with high expression quantity

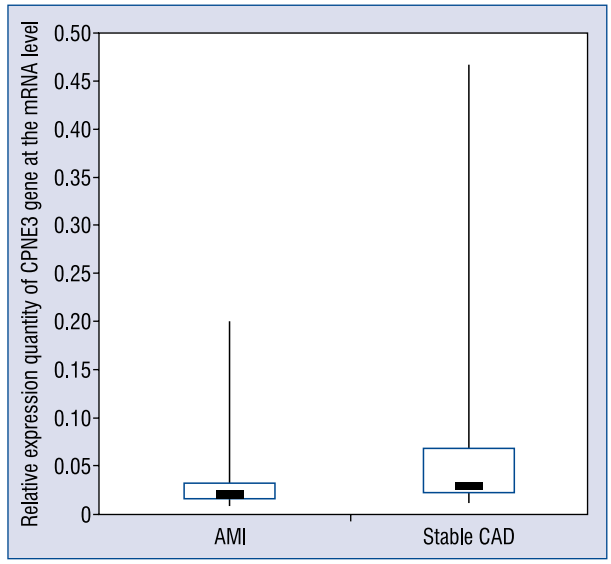

Figure 1. Comparative analysis on relative expression quantity of CPNE3 gene at the mRNA level between the acute myocardial infarction (AMI) group and the stable coronary artery disease (CAD) group.

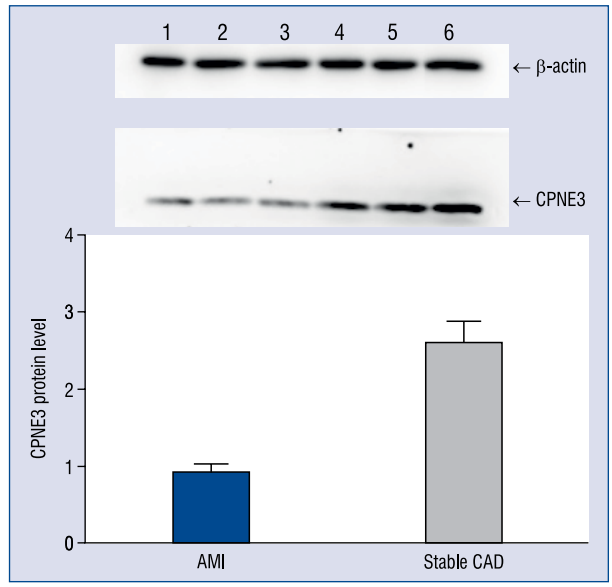

Figure 2. Comparison of expression level of CPNE3 gene at the protein level. For the acute myocardial infarction (AMI) group, sample numbers are 1, 2 and 3; For the stable coronary artery disease (CAD) group, sample numbers are 4, 5 and 6.

($2^{-\Delta Ct} > 0.013$) and a group with low expression quantity ($2^{-\Delta Ct} \leq 0.013$). The result indicates that: Low expression of CPNE3 is a factor closely related with AMI, the OR value increased 3.845 fold respectively. Relatively advanced age is also a factor

Table 3. Analysis on correlation between expression quantity of CPNE3 gene at the MRNA and age of patient, blood glucose, levels of serum TC, HDL-C and LDL-C, ejection fraction of patients.

Group	Number of patients	Relative expression quantity of CPNE3	Z	P
Normal blood glucose	71	0.029 (0.019–0.064)	–0.739	0.460
Increased blood glucose	72	0.024 (0.018–0.045)		
Normal total cholesterol	133	0.025 (0.018–0.048)	–0.554	0.580
Increased total cholesterol	38	0.028 (0.018–0.076)		
Normal triglyceride	101	0.028 (0.019–0.064)	–0.768	0.442
Increased triglyceride	70	0.025 (0.0017–0.043)		
Normal LDL-C	121	0.025 (0.018–0.046)	–0.503	0.615
Increased LDL-C	50	0.030 (0.017–0.084)		
Normal HDL-C	94	0.025 (0.018–0.045)	–1.318	0.188
Decreased HDL-C	77	0.026 (0.018–0.059)		
Younger age	116	0.030 (0.019–0.070)	–2.635	0.008
Advanced age	62	0.022 (0.017–0.030)		
Normal ejection fraction	108	0.026 (0.018–0.042)	–1.434	0.152
Low ejection fraction	23	0.046 (0.021–0.070)		

HDL-C — high density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; TC — total cholesterol

Table 4. Result of logistic regression analysis on independent risk factors of acute myocardial infarction.

	Regression coefficient	Standard error	Wald	P	Odds ratio	95% confidence interval
Low expression of CPNE3 gene	1.347	0.326	17.022	0.000	3.845	2.028–7.292
Relatively advanced age	0.957	0348	7.583	0.006	2.605	1.318–5.149

closely related with AMI, the OR value was 2.605 fold, respectively. Correlation of estimate between low expression and relatively advanced age is (rs = –0.451, p = 0.000; see Table 4 for details).

ROC curve and cut-off value of relative expression quantity of CPNE3 gene in diagnosis of AMI

Based on the relative expression quantity of CPNE3 gene, the $2^{-\Delta Ct}$ value, acquired through PCR, receiver operating characteristic (ROC) curve was created, as indicated in Figure 3. It is known from Figure 3 that the area under curve (AUC) is 0.684 ± 0.040 and the cut-off value of relative expression quantity of CPNE3 gene determined is based on the maximum value of Youden index is 0.024, for which sensitivity and specificity for diagnosis of AMI are 0.690 and 0.648, respectively. Positive predictive value and negative predictive value are 68.6% and 65.2%, respectively (see Figure 3 for details).

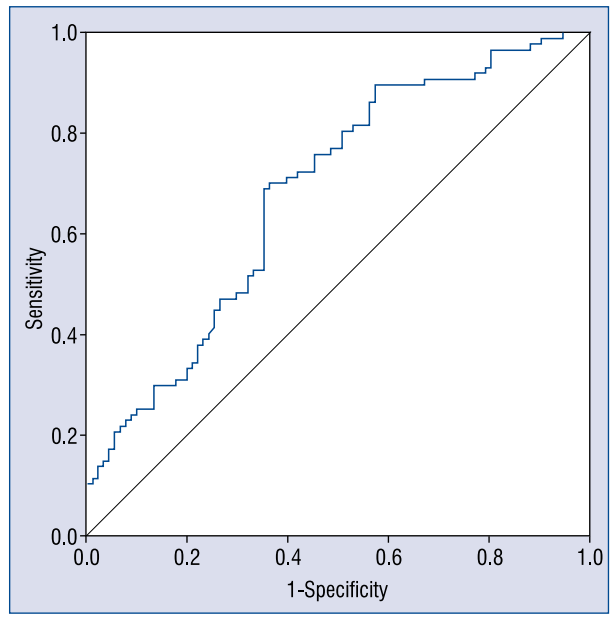

Figure 3. Receiver operating characteristic (ROC) curve CPNE3 gene in diagnosis of acute myocardial infarction. Diagonal segments are produced by ties.

Double-variable correlation analysis between relative expression quantity of CPNE3 gene and degree of severity of coronary artery lesion, cardiac troponin I, interval from timespan of onset of AMI of patients to blood collection

The result of Gensini score of all subjects was 25 (9.5–52). The expression quantity of CPNE3 at the mRNA level was negatively correlated to Gensini score ($rs = –0.200$, $p = 0.018$).

The test result of cardiac troponin for the AMI group is 0.790 (0.138–8.760) ng/mL. Concentration of serum troponin I (TnI) can reflect the scope of AMI. The expression quantity of CPNE3 gene in peripheral blood is unrelated to serum TnI concentration ($rs = –0.144$, $p = 0.364$).

The incipient long-time (≥ 20 min) rest pain of patients suffering from AMI in the last week was considered as the time of onset and the interval from onset of AMI of patients in the AMI group to the time when blood was collected should be the time interval of occurrence, for which the result was 24 (11–72) h. There was no correlation between the expression quantity of CPNE3 gene and timespan ($rs = –0.098$, $p = 0.533$).

Discussion

The role played by the Copine family in cells still remains unknown although some studies have indicated that it might have an influence on membrane protein, lipid and other activities [10]. It has been reported that the interaction between CPNE3 and ErbB2 could promote tumor metastasis, which played a role in non-small cell lung cancer, breast cancer, prostate cancer and ovarian tumor [11, 12, 19]. However, there is no study on the role played by CPNE3 in occurrence and progression of cardiovascular disease. This study focused on investigating the expression quantity of CPNE3 gene in peripheral blood of AMI patients and found that it was significantly lower than that of stable CAD patients at both the mRNA and protein levels.

CPNE3 mRNA expression with clinical variables were correlated, including blood glucose, serum TC, TG, LDL-C or HDL-C, age, and EF. As a result, a significantly different expression of CPNE3 was found between patients with AMI and patients with stable CAD. Further analysis indicated that abnormal expression quantity of CPNE3 gene was irrelevant to EF values. According to a previous study, patients with AMI had a preponderance to develop REF/HFREF due to irreversible myocardial damage. It was particularly true in large transmural/ST-segment elevation myocardial infarction infarcts [20]. Thus, the significant difference of CPNE3 gene expressions in the present study is not due to reduced EF since AMI leads to reduced EF.

Prevalence and fatality rate of AMI was reported to increase with age [21]. Currently, age remained a strong independent predictor of both in hospital and 1-year post-discharge mortality rates in patients with AMI [22]. Binary logistic analysis showed that low expression of CPNE3 gene was an independent risk factor for AMI (OR 3.845; $p < 0.05$) and age also was an independent risk factor for AMI (OR 2.605; $p < 0.05$). Regardless of age and other factors, low expression of CPNE3 gene could increase the risk of AMI in stable CAD patients by 3.845 times. While advanced age of patients alone could increase the risk of AMI by 2.605 times. Thus, it was speculated that older patients who have low CPNE3 expression would be more likely to suffer from AMI.

CPNE3 was shown to participate in immune-regulation and neutrophil degranulation, including metabolism of lipids such as fatty acid, triglyceride, lipoprotein and ketone bodies (from REACTOME). Conventional risk factors of CAD [23–25], hypertension [25], hypercholesterolemia [26], diabetes, [27] obesity, [28] smoking, [25, 29] and family history [30] were believed to have an adverse influence on prognosis in those with established disease, presumably through their effect on the progression of atherosclerotic disease processes. However, the present study demonstrated that low expression of CPNE3 was unrelated to blood glucose, serum TC, TG, LDL-C, and HDL-C. It was speculated that the mechanism of CPNE3's role in promoting AMI may be not through lipid metabolism or blood glucose.

Although the mechanism of CPNE3's role in promoting the occurrence of AMI is still unknown. Results herein indicate that the relative expression quantity of CPNE3 gene is correlated to Gensini score, which defines the severity of coronary artery lesion. Gensini score has been reported to be mainly correlated to the degree of coronary stenosis and scope of blood supply [31]. Therefore, lower expression of CPNE3 may lead to a higher severity of coronary artery lesion.

Quantity of cardiac troponin predicts the extent of myocardial infarction. This study showed that expression quantity of CPNE3 gene was unrelated to a concentration of TnI. Furthermore, the present study indicated that there was also no correlation between the expression quantity of CPNE3 gene

in peripheral blood and timespan of AMI. If a low expression of CPNE3 had occurred with AMI, expression quantity of CPNE3 gene should be correlated to concentration of TnI and the timespan and vice versa. In our case, low expression of CPNE3 gene didn not occur with AMI and thus might serve as one of the causes of AMI which was supported by the ROC curve of CPNE3 mRNA expression in diagnosing AMI.

Therefore, it was speculated that low expression of CPNE3 gene may increase the risk of AMI by promoting formation of coronary artery lesion. Although it is not conclusive if low expression of CPNE3 causes AMI, it is speculated that low CPNE3 expression is a cause of AMI. To confirm this, a prospective randomized study is indispensable. More experiments of CPNE3 functions and investigation of its mechanism of molecular biology are also required.

Conclusions

Acute myocardial infarction patients have the lower expression of CPNE3 gene in their peripheral blood in comparison to stable CAD patients. There is an association between low expression of CPNE3 and AMI. Patients who have a lower CPNE3 expression in peripheral blood are more likely to suffer from AMI than other patients with stable CAD. Low expression of CPNE3 gene serves as a potential independent risk factor of AMI.

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Conflict of interest: None declared

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VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

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Chest pain and plaque rupture without high-sensitive troponin elevation

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A 41-year-old male with established coronary artery disease and previous ST-elevation myocardial infarction requiring treatment of the right coronary artery (RCA) with a drug eluting stent (DES) presented to the emergency department with acute-onset typical angina (Canadian Cardiovascular Society IV). Electrocardiogram and clinical examination were unremarkable. The values of high-sensitivity troponin T drawn at admission (4 h after chest pain onset) and 3 h later were 4 ng/L and 3 ng/L, respectively (99th percentile cut-off value < 14 ng/L). Creatinine kinase-MB and myoglobin remained within normal range as well. Due to the pain characteristics and patient's past history troponin-negative acute coronary syndrome (ACS) (unstable angina) was suspected and early invasive evaluation of his coronary anatomy was undertaken. Left coronary arteries were normal, a patent DES (Fig. 1, arrow) in the proximal RCA, but a hazy-appearing region (Fig. 1, arrowhead) in the mid-RCA was noted. Since this region seemed angiographically inconclusive, an optical coherence tomography (OCT) was performed. This revealed a ruptured plaque with a rupture cavity (Fig. 1, asterisk) at the site of interest (Fig. 1, segments 1–3). The plaque rupture was interpreted as the culprit lesion and was treated with 1 DES. The patient was discharged the following day.

Despite the advent of high-sensitive troponin assays, physicians should still be aware of troponin-negative ACS presentations. As illustrated herein, acute plaque rupture accompanied by acute chest pain does not necessarily result in cardiac necrosis and elevated troponin levels. OCT represents a valuable technology to better understand the underlying pathophysiology and identify the culprit lesion(s) leading to ACS, particularly in patients with inconclusive angiograms.

Conflict of interest: None declared

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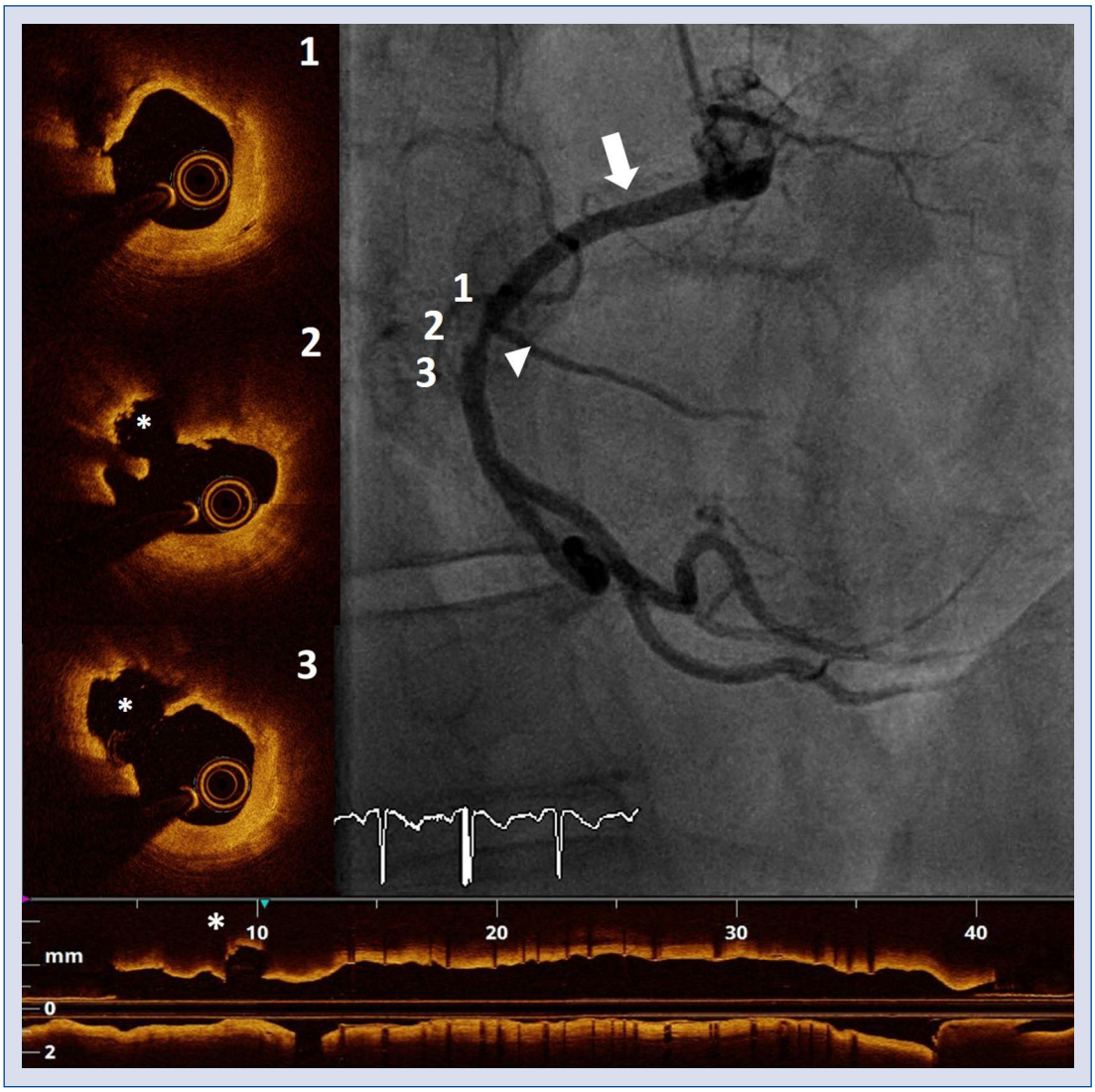

Figure 1. Right coronary artery (RCA) with previously placed drug eluting stent (arrow). Mid-RCA lesion with associated haziness (arrowhead) and corresponding frames from optical coherence tomography (OCT) pullback (1–3) showing plaque rupture and ruptured cavity (*). On OCT minimal luminal area at the culprit site was 3.3 mm^2 and area stenosis 27%. On quantitative coronary angiography minimal luminal diameter was 1.6 mm and degree of stenosis 44%.

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

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Life-threatening acute myocardial infarction due to left main dissection during radiofrequency transcatheter ablation of atrial tachycardia

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A 65-year-old woman was hospitalized for recurrent episodes of atrial tachycardia; echocardiography showed dilated left ventricle with depressed systolic function (ejection fraction 30%), without significant epicardial coronary stenoses at angiography.

An electrophysiological study identified the origin of the arrhythmia in the posterior and mid-septal walls of the right atrium. A radiofrequency transcatheter ablation (RTA) was performed through the right femoral vein approach: the right atrium was reached and a radiofrequency energy application of 35 W was delivered. During an inducibility test the patient complained of retrosternal pain associated with ST elevation in the V1 lead (Fig. 1A–D).

The subsequent emergency angiography showed ostial subocclusion of the left anterior descending (LAD) artery, suggesting a coronary dissection. At the second contrast injection the distal left main (LM) occluded. A percutaneous coronary intervention with a 3.5 × 38 mm zotarolimus-eluting stent implantation at the LAD ostium was performed (Fig. 1E–J). After restoration of a Thrombolysis in Myocardial Infarction (TIMI) flow grade 3 in the LAD, an intravascular ultrasound (IVUS) run revealed a dissection flap at the level of the LM, managed with a second 4.5 × 15 mm zotarolimus-eluting stent implantation. A good angiographic result was confirmed by a final IVUS run that demonstrated correct stent apposition through the LM-LAD axis (Fig. 1K–O). At 1 month follow-up patient's ejection fraction rose to 45%.

According to available research, this is the only case in the literature of life-threatening LM dissection during right atrium RTA through a venous approach in which a fortuitous coronary ostia engagement can definitely be ruled out.

Conflict of interest: None declared

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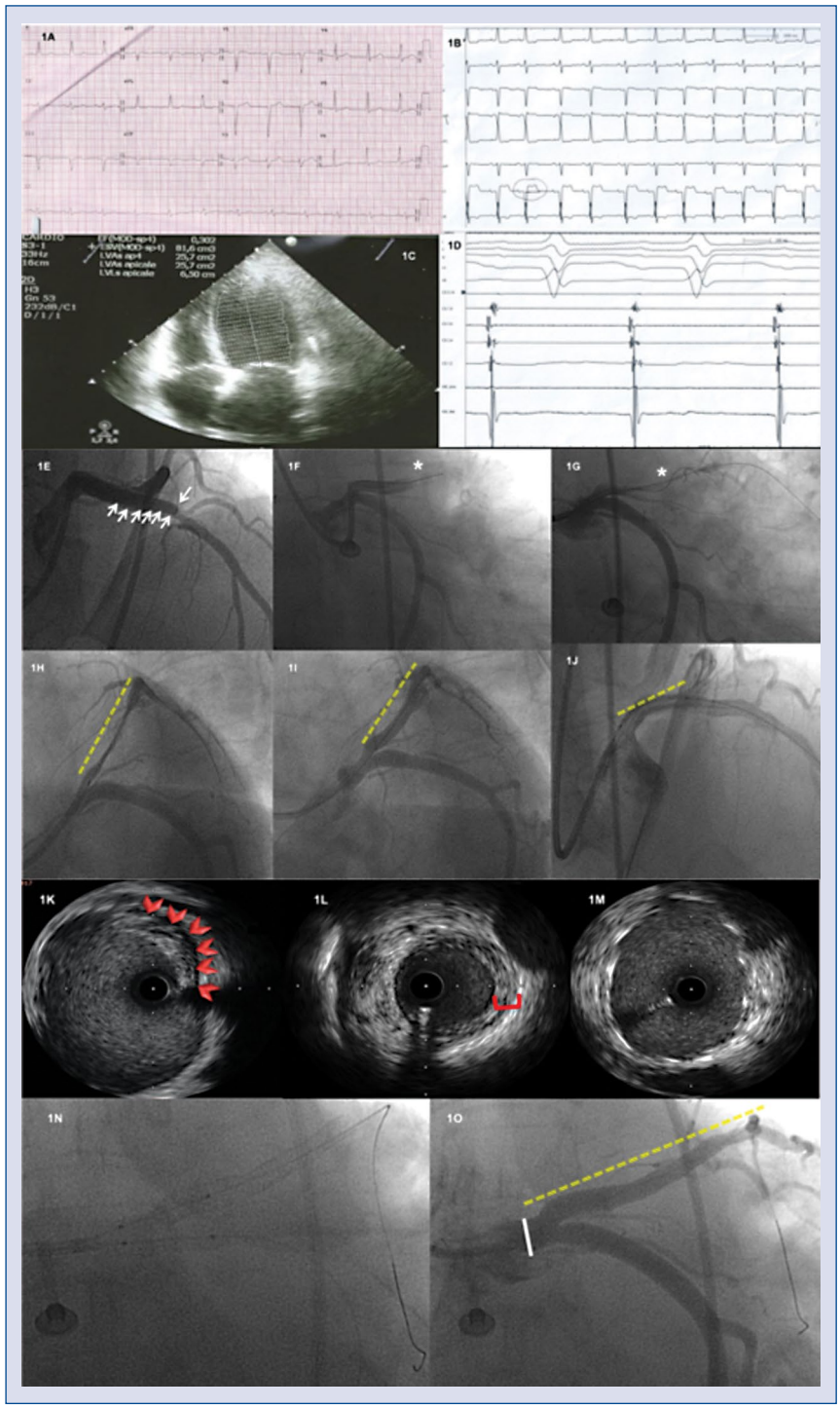

Figure 1. A. Normal electrocardiogram at admission; **B.** Electrocardiogram revealing ST elevation in V1; **C.** Transthoracic echocardiography at admission showing dilated left ventricle with 30% ejection fraction; **D.** Monitor polygraph record during transcatheter ablation; **E.** Left anterior descending coronary artery (LAD) dissection (white arrowheads); **F, G.** Abrupt total LAD closure (asterisks) and guidewire crossing; **H, I.** LAD drug eluting stent (DES) positioning and implantation (yellow dashed lines); **J.** DES positioning on left main (LM)-LAD (yellow dashed lines); **K, L, M.** Intravascular ultrasound (IVUS) run: IVUS images showing the extension of the dissection flap at the level of the LM (K: red arrowheads) and the optimal stent covering after stenting (M). IVUS at the level of the mid LAD shows medial thickening (L: between brackets); **N:** Final optimization with kissing balloon technique; **O.** Final angiographic result after LM-LAD percutaneous coronary intervention with DES implantation (yellow dashed lines).

VIA MEDICA

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Successful primary percutaneous coronary intervention in patient with ST-segment elevation myocardial infarction via left snuffbox approach: Patient advantages

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A 40-year-old man was referred to the documented institute with evidence of ST-segment elevation in the anterior electrocardiogram leads. Urgent coronary angiography (CAG) was performed via the left snuffbox approach using 6 Fr sheath (Fig. 1A) with loading of acetylsalicylic acid 300 mg and prasugrel 60 mg. After administration of 3000 units unfractionated heparin via sheath, CAG demonstrated total occlusion in the proximal left anterior descending artery (LAD) (Fig. 1B). Primary percutaneous coronary intervention (PCI) was successfully performed with a 3.25 × 23 mm everolimus-eluting stent after intracoronary bolus of abciximab (Fig. 1C). Hemostasis was obtained by compressive bandage method after PCI and he was moved to the coronary care unit (CCU). There was no puncture site complication after hemostasis for 3 h (Fig. 1D) and the patient did not complain about an inconvenience of finger or wrist movement in the puncture side hand after removal of the sheath (Fig 1E). Post-PCI echocardiography demonstrated hypokinesia of the anterior wall with good left ventricular systolic function. Two days subsequent to PCI, including a 1-day CCU and 1-day ward care, the patient was discharged without any sequelae.

As shown in Figure 2, there are 2 snuffbox puncture sites where well pulsation of the distal radial artery can be found. One is located in the anatomical snuffbox and the other is in the first intermetacarpal space, which is the proximal area from Trapezoid and Trapezium [1]. Data regarding the snuffbox approach remains limited, but published data and cases supporting that snuffbox approach could be considered as an alternative access site in selected patients, such as patients with high bleeding risk or renal impairment [2, 3]. Especially, the left snuffbox approach might be useful for elderly patients due to less subclavian tortuosity when compared with the right radial approach [4]. In terms of feasibility of the snuffbox approach for primary PCI, prospective studies are needed to confirm safety and efficacy as there has been only 1 case report published [5]. Furthermore, there are no data regarding the benefit of the snuffbox approach for early discharge, even though current guidelines support that early discharge, within 48–72 h, should be considered in selected low-risk patients with ST-segment elevation myocardial infarction (STEMI) after successful primary PCI. This case illustrates the potential benefits of the snuffbox approach regarding hemostasis and early mobilization leading to the early discharge after successful primary PCI in the low-risk patient with STEMI.

Conflict of interest: None declared

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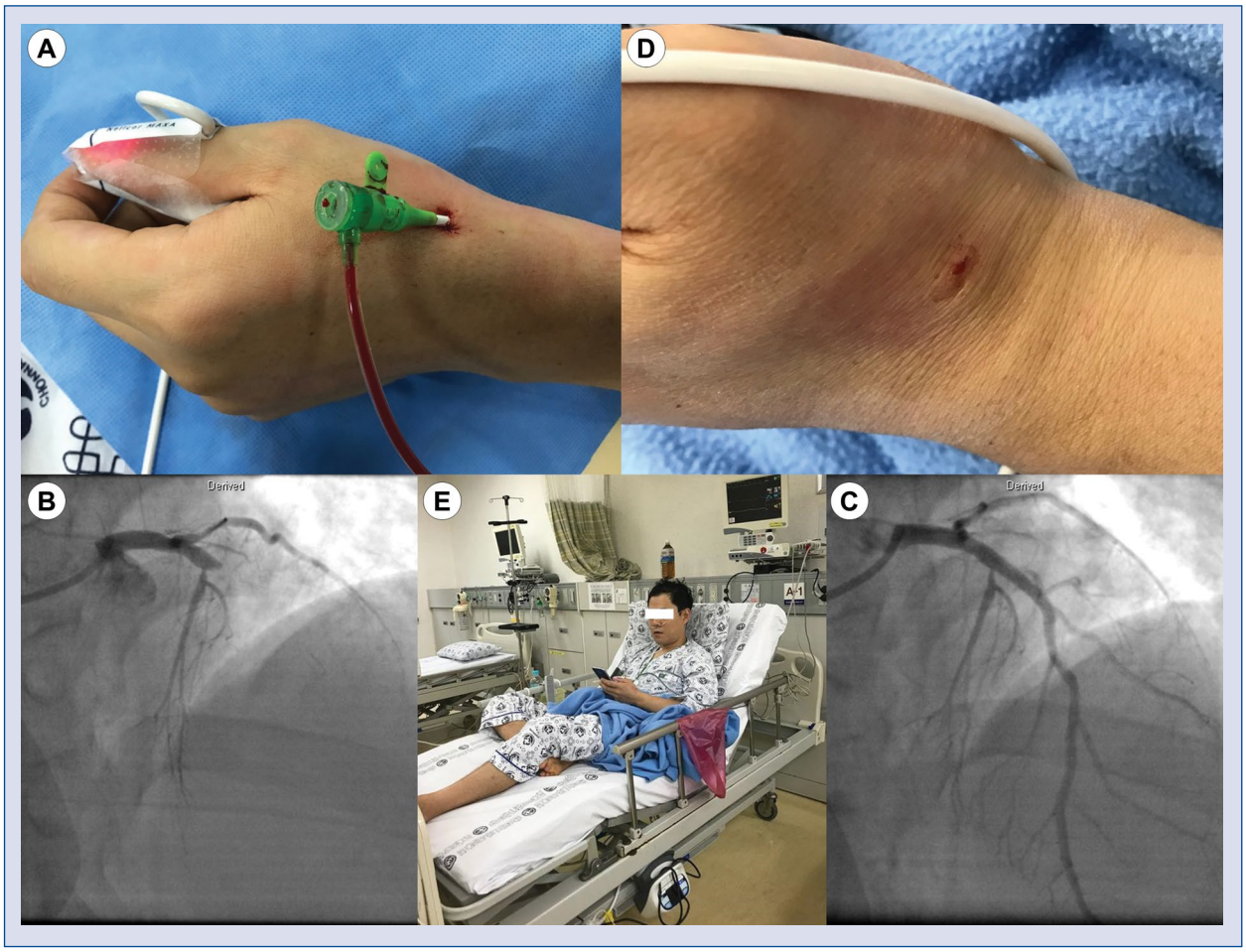

Figure 1. A. Inserted 6 Fr sheath via left snuffbox approach; **B.** Urgent coronary angiography (CAG) demonstrating thrombotic total occlusion in the proximal left anterior descending artery; **C.** CAG demonstrating successful primary percutaneous coronary intervention with drug-eluting stent implantation; **D.** No bleeding complication of puncture site after 3-hour hemostasis; **E.** Patient using a mobile phone without the inconvenience of puncture-side hand immediately after removal of sheath.

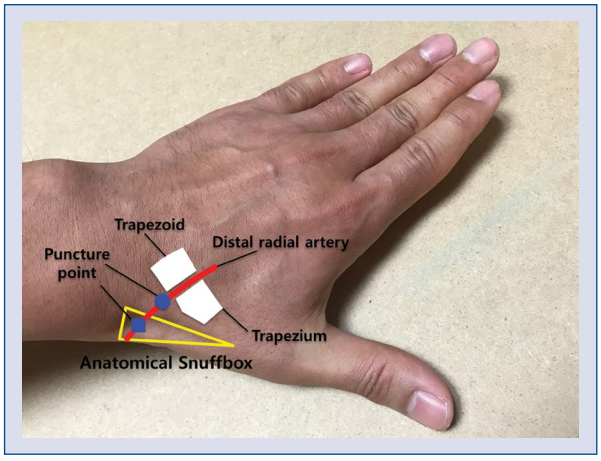

Figure 2. Snuffbox puncture sites in the anatomical snuffbox (blue box) and in the first intermetacarpal space (blue circle).

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VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

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Large calcific mass embolization during transfemoral aortic valve implantation

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In a 82-year-old female a 22-mm stented Soprano (Sorin Biomedica Cardio, Saluggia, Italy), bioprosthesis dysfunction was documented. Computed tomography angiography (CTA) showed diffuse aortic calcifications and the presence of an aberrant right subclavian artery or arteria lusoria (AL) (Fig. 1A–D). A valve-in-valve transcatheter aortic valve implantation (TAVI) with a 26-mm Corevalve Evolut R (Medtronic, Minneapolis, MN, USA) was performed via transfemoral access. Due to blood loss, CTA was required; aside a retroperitoneal hematoma, a large calcified plaque, previously undetected at the thoraco-abdominal passage was unexpectedly detected (Fig. 1E, F), causing a 50% caliber reduction.

A careful review of a previous CTA suggested the migration of a voluminous calcification from the aortic arch, likely during system advancement. Since the patient was asymptomatic, a conservative approach was recommended.

Six months later another CTA confirmed the entrapment of the calcified plaque in the descending aorta (Fig. 1G) without clinical signs of peripheral hypoperfusion.

Systemic embolization during TAVI remains a major issue and the protective role of filters for cerebral protection is controversial. Peripheral embolization is considered a "minor" complication, and, in the described case, the dimension of plaque caused its entrapment without clinical consequences. Its fracture could have provoked migration toward more "sensible" districts, e.g. causing visceral or limb ischemia. With the exponential growth of TAVI, nowadays proposed also to treat younger patients and lower risk populations, a careful evaluation of the embolic risk and the development of dedicated algorithms should be advocated.

Conflict of interest: None declared

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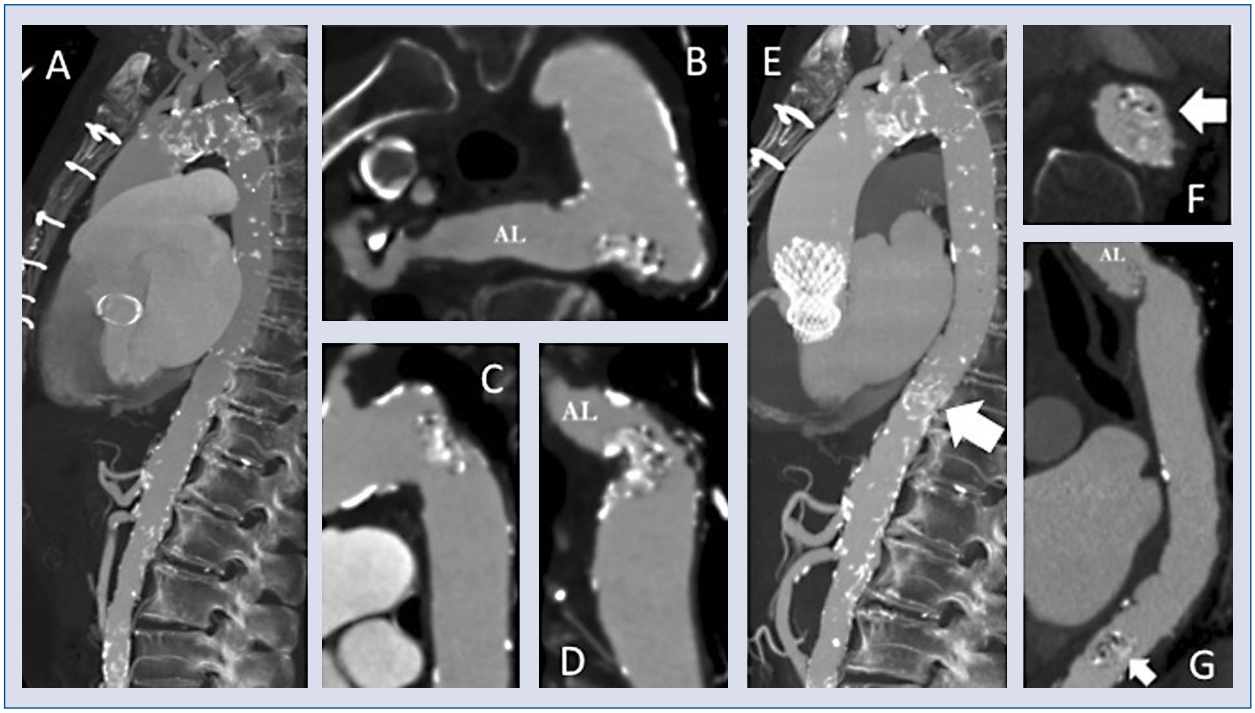

Figure 1. Maximum intensity projection (MIP) documents a severely calcified aortic arch (**A**). multi planar reformation (MPR) images show an arteria lusoria (AL) in axial (**B**) and large calcifications of aortic arch in sagittal (**C**) and coronal (**D**) views. After transcatheter aortic valve implantation (**E**), MIP shows the presence of previously undetected calcifications at the thoraco-abdominal district (arrow), with a bulk mass entrapped in the descending aorta (computed tomography axial scan, **F**), later confirmed at computed tomography angiography performed at 6-month follow-up (coronal view, **G**).

VIA MEDICA

IMAGE IN CARDIOVASCULAR MEDICINE

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Many disorders of one heart: Accidentally discovered aortic dissection, bicuspid aortic valve and hypertrophic cardiomyopathy in young patient with hypertension

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A 29-year-old male with history of hypertension, hospitalized for few days in a local hospital due to pneumonia, was referred to our institution with suspicion of myocarditis and hypertrophic cardiomyopathy. On admission the patient suffered from dyspnea and cough. He denied chest pain. Physical examination revealed only bilateral rales. The baseline level of C-reactive protein was 4.4 (range 0–0.5) mg/dL, high-sensitivity cardiac troponin T was 324 (range 0–14) ng/L, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 3285 (range 0–125) pg/mL. The standard 12-lead electrocardiogram demonstrated sinus rhythm, left atrial enlargement and left ventricular (LV) hypertrophy with non-specific ST segment and T-wave abnormalities (Fig. 1A). The chest X-ray showed bilateral lung consolidation and pulmonary congestion (Fig. 1B). Transthoracic echocardiography revealed significant asymmetric LV hypertrophy with preserved LV ejection fraction, bicuspid aortic valve with moderate regurgitation, and mild dilatation of the ascending aorta (41 mm). Due to suspicion of myocarditis, cardiac magnetic resonance imaging was performed. Hypertrophic cardiomyopathy with a maximal LV wall thickness of 32 mm and increased myocardial mass (LV mass index 149 mL/m^2, range 68–103 mL/m^2) was demonstrated. Moreover ascending aortic dissection was detected (Fig. 1C, D). Computed tomography confirmed aortic dissection originated in the aortic root and involving descending aorta (DeBakey Type I) (Fig. 1E, F). Patient underwent the Bentall procedure and subsequently recovered well from surgery. Aortic dissection typically presents with tearing chest pain and severe hemodynamic compromise. Painless dissection, as in this case, is relatively rare.

Conflict of interest: None declared

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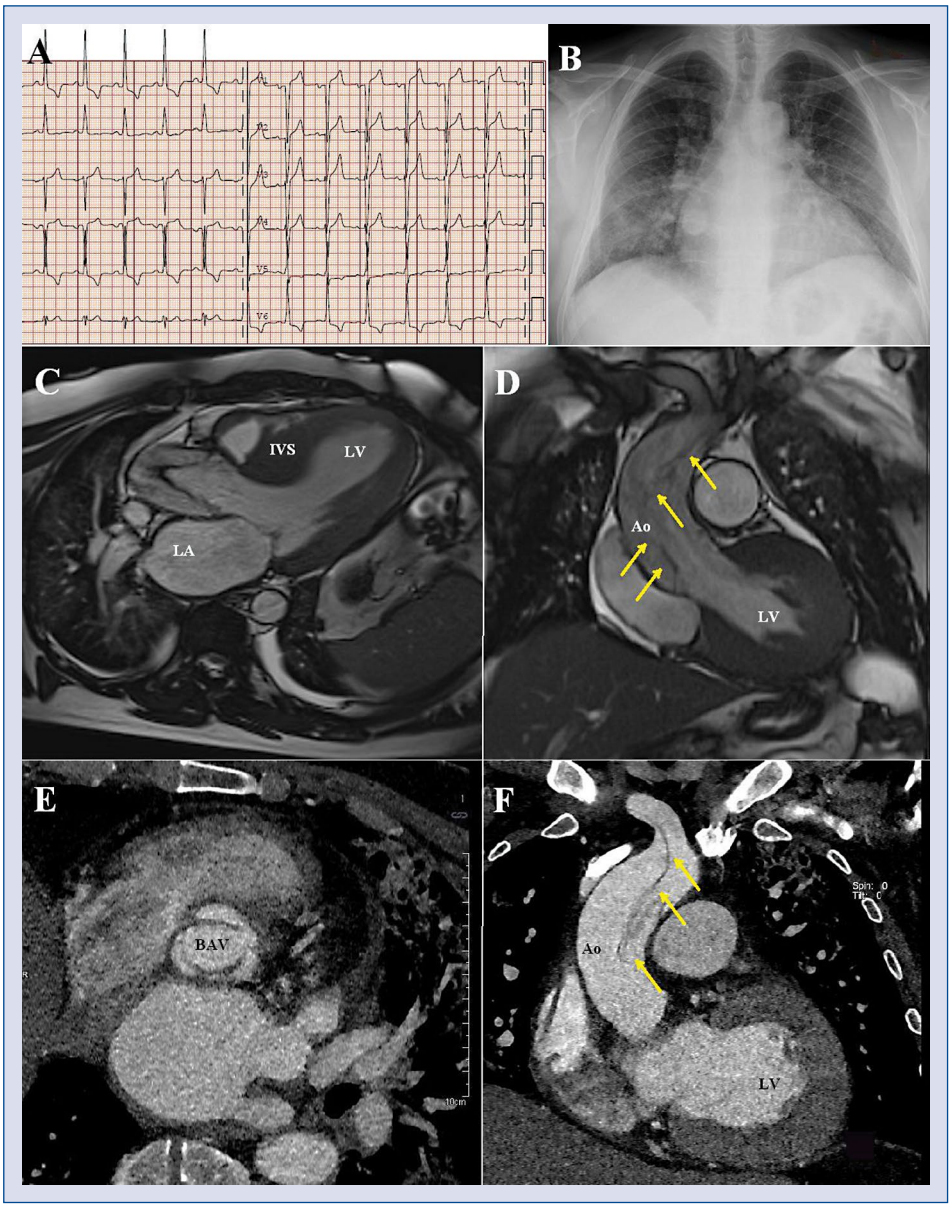

Figure 1. A. Standard 12-lead electrocardiogram; **B.** Chest X-ray; **C.** Cardiac magnetic resonance scans showing hypertrophic cardiomyopathy and **D** — aortic dissection; **E.** Computed tomography scans showing bicuspid aortic valve and **F** — aortic dissection. Ao — aorta; BAV — bicuspid aortic valve; LA — left atrium; LV — left ventricle; IVS — interventricular septum; arrows show dissection flap.

VIA MEDICA

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Always look at both sides of the heart: A double-orifice mitral valve discovered in a young adult with repaired tetralogy of Fallot

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An 18-year-old male with a history of tetralogy of Fallot repair when he was an infant was referred from the aforementioned pediatric center. He reported excellent exercise tolerance. On the physical examination no signs of heart failure were found. A transthoracic echocardiographic study showed preserved function of the enlarged right ventricle (Fig. 1A) and moderate pulmonary insufficiency (Fig. 1B). In addition, two-dimensional echocardiography in the parasternal short axis view (Fig. 1C) and three-dimensional (3D) transthoracic imaging (Fig. 1D) revealed that the mitral valve was divided with a fibrous bridge in two orifices of equal size (double-orifice mitral valve [DOMV]). Neither regurgitation nor obstruction of the valve was found (Fig. 1E, F). No other left-sided heart abnormalities were identified. The patient was submitted to routine clinical follow-up. The presentation of DOMV in adulthood is very rare. The anomaly might be isolated, but usually it coexists with endocardial cushion defects or left-side heart anomalies. DOMV associated with tetralogy of Fallot is an extremely unusual combination of congenital malformations. According to the classification proposed by Trowitzsch in 1985, in the presented case, the most commonly seen echocardiographic form of DOMV, i.e. complete bridge, was diagnosed. 3D echocardiography helps to assess mitral valve morphology and in the current case the transthoracic 3D imaging was sufficient to determine the type of malformation. The case stresses the importance of careful imaging in adult congenital heart disease patients even if transferred from paediatric centres. It is noteworthy to be surprised.

Conflict of interest: None declared

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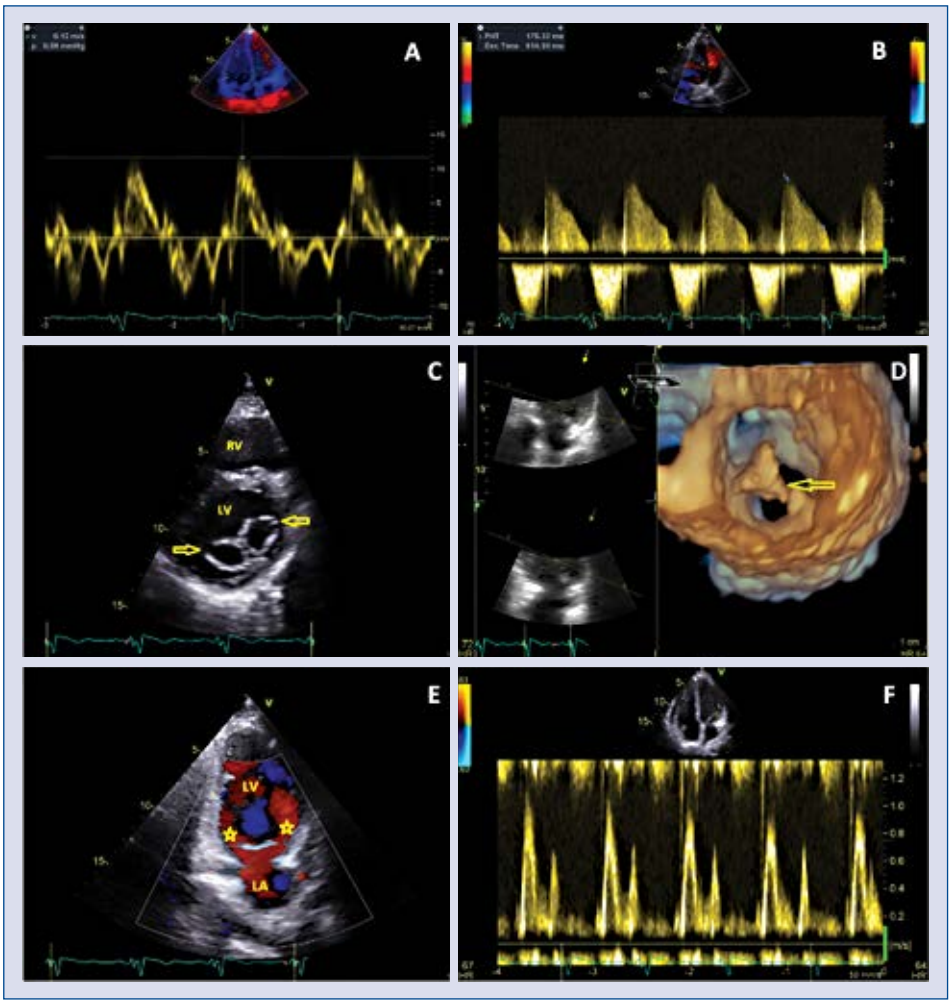

Figure. 1. Two-dimensional and three-dimensional (3D) echocardiographic study of a patient with repaired tetralogy of Fallot and newly diagnosed double-orifice mitral valve. Tissue Doppler imaging in the apical four-chamber view revealed preserved function of the enlarged right ventricle (**A**). In a parasternal short axis view a color Doppler guided continuous wave regurgitant pulmonary flow of moderate degree was also recorded (**B**). **C.** Parasternal short axis view in transthoracic echocardiography. Two separate mitral valve orifices of equal size were observed (arrows). **D.** Transthoracic 3D image of mitral valve. Mitral valve orifice divided by bridging structure clearly demonstrated at the left ventricular view (arrow). **E.** Color Doppler flow velocity mapping in an apical view demonstrated two separate jets of left ventricular filling (asterisks). Pulsed wave Doppler imaging confirmed unrestricted opening of the valve (**F**); LA — left atrium; LV — left ventricle; RV — right ventricle.

VIA MEDICA

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BRIEF COMMUNICATION

Confirmation of jailed side-branch ostium in coronary bifurcation intervention by stent-oriented three-dimensional intravascular ultrasound

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The confirmation of jailing type and rewiring position on the side-branch ostium (SBO) by the three-dimensional (3D) optical coherence tomography (OCT)/optical frequency domain imaging (OFDI) is reported to lead to good stent apposition in percutaneous coronary intervention (PCI) for bifurcation lesion [1–3].

The technology of intravascular ultrasound (IVUS) is advancing, AltaView and VISICUBE (a high-definition IVUS imaging catheter and console, TERUMO, Tokyo, Japan) has an ultrasound frequency of 40 or 60 MHz, a maximum frame rate of 90 frames/s, and a maximum pullback speed (PBS) of 9 mm/s. Generally, a faster PBS reduces motion artifacts, but becomes a frame pitch wider. Because of its high frame rate, the narrowest frame pitch at maximum PBS of AltaView and VISICUBE is 0.1 mm/frame, which is the same as a frame pitch of OCT/OFDI that can make stent-enhanced 3D--images [1]. In this case a 3D-reconstructed IVUS image was made that could confirm jailing type and rewiring position on the jailed SBO.

A 2-link 8-crown bioresorbable polymer sirolimus-eluting stent (Ultimaster Tansei, TERUMO) was simply deployed on a coronary artery in the present clinical case. To segment the vessel lumen, a flushing of blood cells by contrast medium was undergone at image collecting by AltaView (a setting of 60 MHz, 90 frames/s, and PBS 9 mm/s). The IVUS image data was transferred to an offline Windows computer as an audio video interleaving (AVI) format using a universal serial bus (USB) flush drive. This image file was a compressed AVI format, converted to an uncompressed AVI format using the freeware AviUtl version 1.00 [4], and converted to a stacked tagged image file format (TIFF) using the freeware ImageJ 1.43v [5]. Initially, the 3D-IVUS was simply reconstructed from the original IVUS images (stacked TIFF) (Fig. 1A). Confirmation of struts and links in the original 3D--IVUS was difficult because of the blooming effect of strut signals. ImageJ can process various filters for images. The minimum filter does grayscale erosion by replacing each pixel in the image with the lowest pixel intensity in that pixel's neighborhood [5, 6]. Strut signals in the original IVUS images were eroded by the minimum filter, and the stent-oriented 3D-IVUS was reconstructed from these minimum-filtered IVUS images (Fig. 1B). No fused strut images in the stent-oriented 3D-IVUS were seen, and struts and links could be well confirmed. It took about only 5 min from export of the IVUS image data to observation of the stent-oriented 3D-IVUS.

In another clinical case (Fig. 1C), Ultimaster Tansei was deployed from proximal to distal main vessel of a bifurcation lesion, and the guidewire was recrossed to the side-branch. The stent-enhanced 3D-OCT [6] of the jailed SBO is shown in Figure 1D. Using the stent-oriented 3D-IVUS, the jailing type and rewiring position on the jailed SBO could be confirmed as a link-connecting type and proximal rewiring (Fig. 1E) [1–3].

Intravascular ultrasound cannot detect struts unlike OCT/OFDI, and the stent-oriented IVUS simply makes it easier to confirm stents. Linear-link type stents such as Xience Sierra (Abbott Vascular, Santa Clara, CA, USA) may be easy to con-

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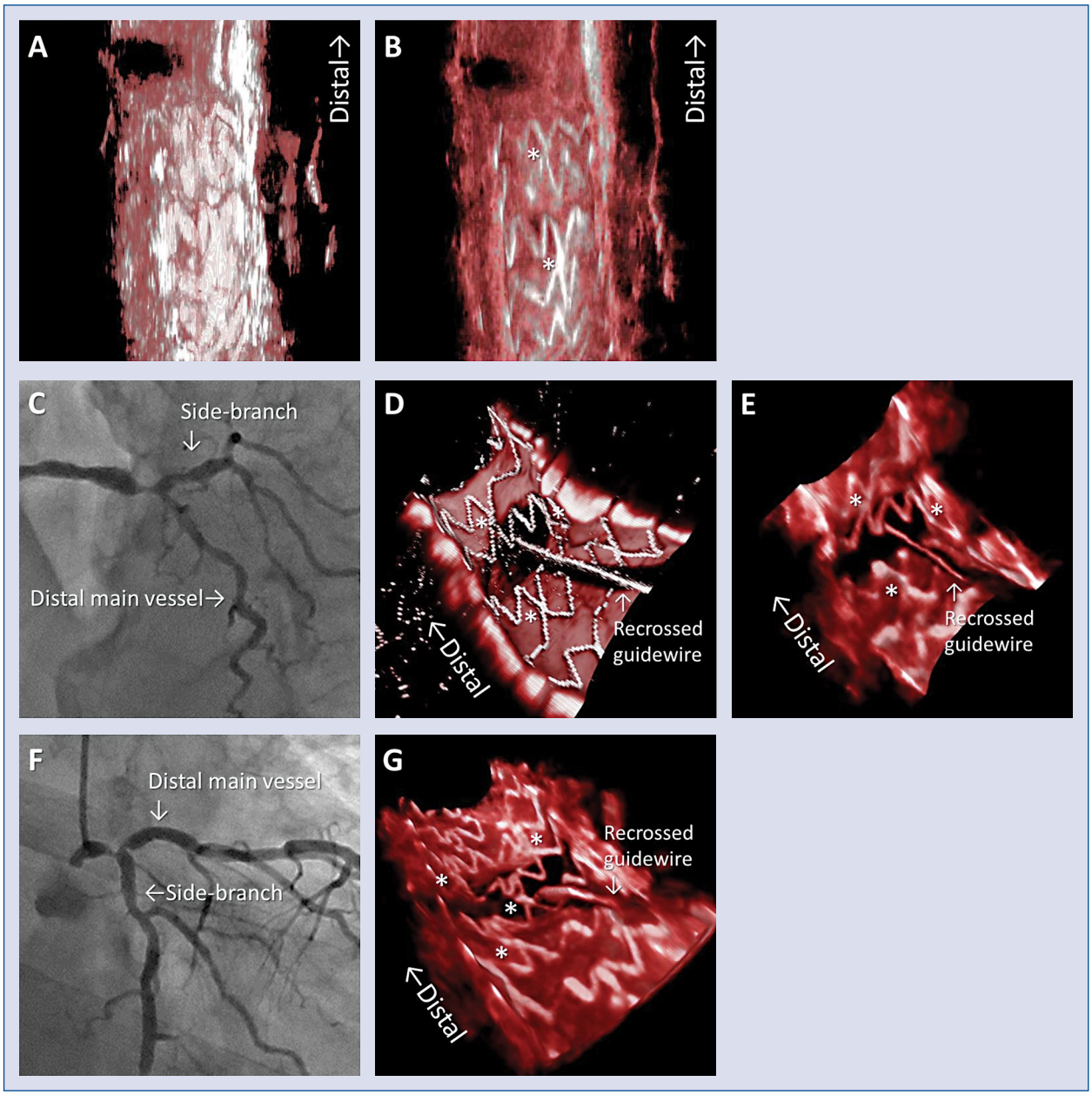

Figure 1. The stent-oriented three-dimensional (3D) intravascular ultrasound (IVUS). **A.** The longitudinal cut-away view of the 3D-IVUS reconstructed from the original IVUS images; **B.** The longitudinal cut-away view of the stent-oriented 3D-IVUS reconstructed from the minimum-filtered IVUS images. The baseline coronary angiogram (**C**), the longitudinal cut-away view of the stent-enhanced 3D optical coherence tomography (**D**) and the stent-oriented 3D-IVUS (**E**) of another clinical case (the crossover stent deployment on the bifurcation lesion with Ultimaster Tansei followed by guidewire recrossing). The jailing type and rewiring position can be confirmed by the stent-oriented 3D-IVUS as the link-connecting type and proximal rewiring. The baseline coronary angiogram (**F**) and the longitudinal cut-away view of the stent-oriented 3D-IVUS (**G**) of a clinical case with Xience Sierra (the crossover stent deployment on the bifurcation lesion followed by guidewire recrossing). Asterisks indicate stent links.

firm their links in a 3D-image reconstructed from sectional images because of longitudinally long links (Fig. 1F, G). Peak-to-valley type stents such as Ultimaster Tansei may be useful for the stent-oriented 3D-IVUS even if they are the point-link type, because their adjacent struts, excluding those that are a link part, are apart from one another. In stent-oriented 3D-IVUS, flushing of blood cells by contrast medium is required to segment the vessel lumen, and flushing speed of contrast medium

is the same as OCT/OFDI (3.5–4.0 mL/s). Since only flushing of blood cells around the bifurcation is required, the amount of contrast medium for flushing in the stent-oriented 3D-IVUS is 5–10 mL and less than that in OCT/OFDI. Flushing of blood cells by low-molecular-weight dextran lactate may substitute for that by contrast medium [7], and the confirmation of the vascular lesion and the stent apposition in IVUS-guided PCI does not require flushing of blood cells basically. Most coronary interventional cardiologists are familiar with IVUS as an economical intravascular imaging devise. Adding this option (the 3D-reconstruction of the minimum-filtered IVUS images) to the IVUS console may result in good stent apposition on the SBO in IVUS-guided bifurcation PCI.

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VIA MEDICA

LETTER TO THE EDITOR

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Fully bioresorption of an Absorb bioresorbable vascular scaffold after scaffold restenosis

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A 72-year-old man with hypertension, dyslipidemia, diabetes mellitus and atrial fibrillation underwent coronary angiography due to unstable angina in 2012. A two-vessel disease was found and percutaneous coronary revascularization was performed. Mid left anterior descending (LAD) and distal right coronary artery (RCA) were treated with 3 × 28 mm and 2.5 × 18 mm bioresorbable vascular scaffolds, respectively (Absorb BVS, Abbott Vascular, Santa Clara, CA, USA). Although this was probably not the best case for bioresorbable scaffold implantation, Absorbs BVS were used due to the apparent technical simplicity of these two lesions and the hypothetical benefit of bioresorbable technology in case of future anastomosis of bypass grafts. Pre-dilatation and high pressure post-dilatation were performed with non-compliant balloons in both cases. The final result was evaluated with optical coherence tomography (OCT), which showed a short segment of mild underexpansion in RCA (minimal scaffold area after post dilation 4.01 mm^2) and an optimal result in LAD (Fig. 1, Panels A-1.1, A-1.2, A-1.3). The patient was discharged 4 days later on dual antiplatelet therapy, beta-blockers, angiotensin-converting enzyme inhibitors and statins.

Six months later, the patient was readmitted due to a new episode of unstable angina. A new coronary catheterization showed a restenosis of the distal RCA scaffold, without restenosis of LAD BVS or any other coronary lesion. BVS restenosis was pre-dilated with an AngioSculpt balloon (AngioScore, CA, USA); then, a 2.5 × 28 mm everolimus-eluting stent (Xience, Abbott Laboratories, Abbott Park, IL, USA) was implanted. An OCT analysis was performed before and after drug-eluting stent (DES) implantation and showed that restenosis was located at the zone of the initial under-expansion (Fig. 1, Panels A-2.1, A-2.2, A-2.3).

The patient underwent left atrial appendage closure and pacemaker implantation in 2014. In 2017, he was again readmitted to hospital complaining of dyspnea and atypical chest pain. Due to his past medical history, he underwent a new coronary catheterization in order to discard a new restenosis or coronary lesion. There was no evidence of new lesions or restenosis after coronary angiography, so a new OCT analysis was performed over the scaffolded segments of RCA and LAD.

Bioresorbable vascular scaffold were completely reabsorbed in both LAD and RCA with adequate development of a new neointimal layer. A signal-rich layer development was observed in LAD, which corresponds to neointima and underlaying tissue in OCT image (Fig. 1, Panels B-3.1, B-3.2, B-3.3). On the other hand, this pattern was not seen in RCA because of the previously implanted DES. In this case, and thanks to BVS bioresorption, RCA looked like a common stented artery evaluated by OCT after metallic stent endothelization (Fig. 1, Panels A-3.1, A-3.2, A-3.3).

Absorb BVS was one of the first bioresorbable scaffolds to be developed and it was ready for use in most European countries in 2012 [1]. The first studies showed good long-term outcomes with this device [2, 3], but safety has been questioned re-

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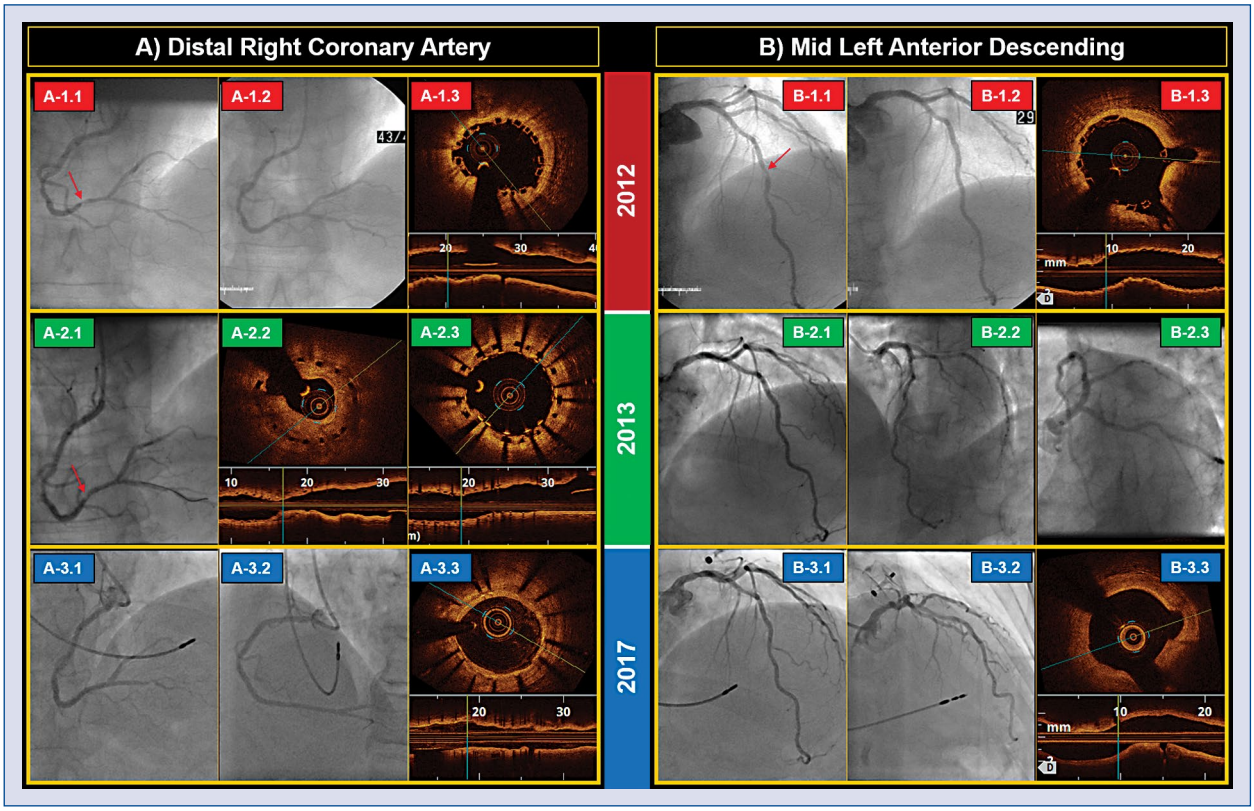

Figure 1. Coronary angiography and optical coherence tomography (OCT) findings after scaffold implantation. **A.** Right coronary artery (RCA): **A-1.1.** A severe lesion of distal RCA (red arrow); **A-1.2.** Result after scaffold implantation; **A-1.3.** Under-expanded Absorb by OCT. **A-2.1.** A severe in-bioresorbable scaffold implantation (BVS) restenosis in distal RCA (red arrow); **A-2.2, A-2.3.** OCT findings before and after restenosis treatment with drug-eluting stent implantation. **A-3.1**, **A-3.2, A-3.3.** Angiography and OCT findings at 5-year follow-up. **B.** Left anterior descending (LAD): **B-1.1.** Severe lesion of mid LAD (red arrow); **B-1.2.** Result after scaffold implantation; **B-1.3.** Normal position of scaffold by OCT. **B-2.1**, **B-2.2, B-2.3.** Normal coronary angiography without BVS restenosis in 2013. **B-3.1**, **B-3.2, B-3.3.** Angiography and OCT findings at 5-year follow-up.

cently. In this regard, differing long-term follow-up trials suggest that BVS is associated with a higher incidence of thrombosis and myocardial infarction [4–6]. However, these adverse results may be related to an improper implantation technique and some technical aspects of the scaffold itself such as large profile, thick stent strut, scaffold deformation during the resorption period, and other issues [7]. In this context, intensive research is ongoing worldwide to clarify the importance of implantation technique for long-term results of this scaffold in the real world [8]. Nonetheless, there is not enough information about BVS bioresorption apart from ABSORB studies. BVS bioresorption has only been demonstrated in vivo by OCT after long-term follow-up in cohort A and B of the ABSORB studies [9, 10]. In this case, OCT findings after 5-year follow-up of actual patients previously treated with Absorb BVS and complicated with early scaffold restenosis, only one of them showed full reabsorption of both BVS.

In summary, fully bioresorption of Absorb BVS was found at 5-year follow-up in both scaffolded arteries, regardless of in-BVS restenosis. After scaffold resorption, an adequate healing process with signal-rich development was observed in LAD, while this pattern was less evident in RCA because of the previously implanted DES. In this context, DES implantation is a good therapeutic option for BVS restenosis.

Conflict of interest: None declared

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LETTER TO THE EDITOR

A giant coronary artery aneurysm and recurrent ST-segment elevation myocardial infarction: A management dilemna

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Giant coronary artery aneurysms (CAA), generally described as dilation that exceeds the reference vessel diameter by 4 times [1, 2], are a rare phenomenon and therefore the optimal management strategy in these clinical scenarios remains controversial without available evidence-based guidelines. CAA treatment options may include conservative medical therapy, percutaneous coronary intervention (PCI), and surgical revascularization [2]. Herein, is described the dilemma of managing an acute occlusion of a proximal left anterior descending artery (LAD) giant CAA, where each of the described treatment strategies were utilized in succession, ultimately leading to successful surgical intervention after the failure of less invasive medical and percutaneous methods.

A 50-year-old male was referred to the documented department after presenting high lateral ST-segment elevation myocardial infarction (STEMI). Coronary angiography revealed diffuse atherosclerosis and aneurysmal coronary arteries, notable for a giant proximal LAD coronary aneurysm with a hazy filling defect at the distal aneurysm edge and Thrombolysis in Myocardial Infarction (TIMI) grade 2 flow (**Suppl. Movie 1**). Left ventriculography confirmed the presence of an anterolateral wall motion abnormality (calculated left ventricular ejection fraction [LVEF] of 50%). Due to resolution of patient symptoms in the catheterization laboratory, in the context of angiographic findings, intervention was deferred in favor of a conservative treatment strategy. The patient was treated with triple anti-thrombotic therapy including acetylsalicylic acid (ASA), clopidogrel, and warfarin with a goal international normalized ratio (INR) of 2.0–3.0. Four months after discharge, warfarin was switched to rivaroxaban (20 mg per day) because of persistent subtherapeutic INR levels.

The patient remained clinically well until 10 months after his initial presentation, when he developed sudden-onset recurrent chest pain. Initial electrocardiogram (ECG) revealed an acute anterior STEMI. Emergency coronary angiography was performed within 6 h of symptom onset and demonstrated thrombotic occlusion of the proximal LAD inside the aneurysm (Fig. 1A). Left ventriculography showed a new, severely reduced ejection fraction (calculated LVEF of 28%) with marked hypokinesis of the anterior segments. An urgent Heart Team meeting between interventional cardiology and cardiac surgery was assembled, and a consensus decision was to proceed with primary angioplasty in the context of STEMI. Bolus IV heparin was given and the activated clotting time remained at > 350 s throughout the case indicating adequate systemic anticoagulation. Following engagement of the left main coronary artery with a 6 French EBU 4.0 guiding catheter, an intracoronary abciximab bolus (0.25 mg/kg body weight) was immediately administered. The LAD occlusion was crossed using a Sion blue wire (Asahi Intecc, Nagoya, Japan) with difficulty due to the aneurysmal sac. Primary angioplasty at the site of occlusion with a compliant balloon (Ryujin™

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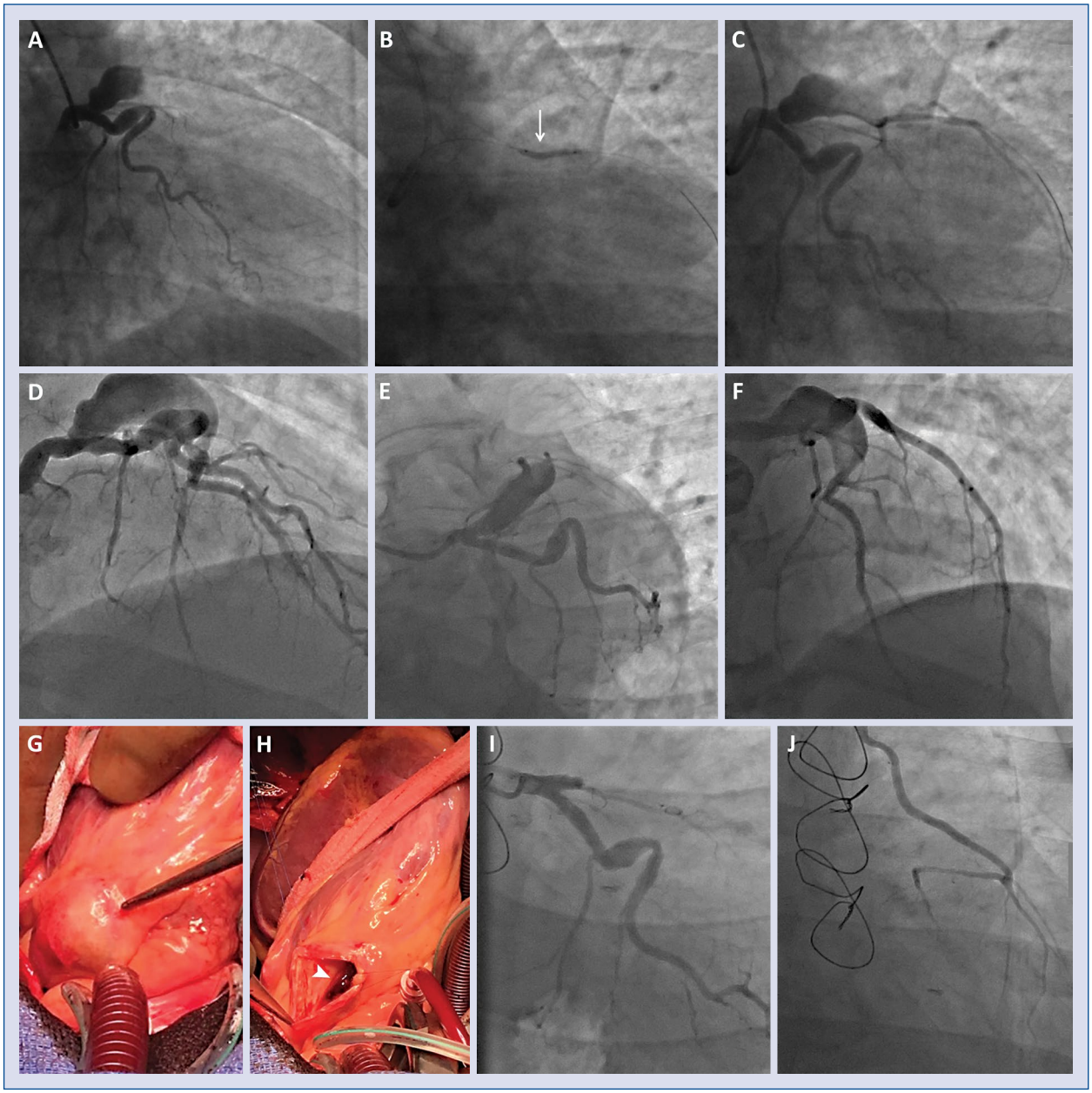

Figure 1. Emergent coronary angiography demonstrated occlusion of the proximal left anterior descending artery (LAD) inside the aneurysm (**A**). The balloon inflation clearly revealed the distal funnel of the aneurysm: there was a 20° angle (arrow) between the intra-aneurysm portion and the extra-aneurysm portion of the balloon inside the LAD (**B**). Primary angioplasty at the site of occlusion restored Thrombolysis in Myocardial Infarction (TIMI) grade 2 flow into the distal LAD (**C**). Six days later, a repeat coronary angiography confirmed partial regression of the thrombus in a patent LAD with TIMI grade 3 flow (**D**, **E**, **F**). Then, the Heart Team decision was to proceed with cardiothoracic surgery combining aneurysm exclusion and coronary artery bypass graft. During surgery the aneurysm was opened showing residual thrombus inside (arrowhead; **G**, **H**). Control coronary angiography revealed a total exclusion of the aneurysm (**I**) and final good result of the left internal mammary artery bypass grafting (**J**).

Plus, 2.0 × 15 mm, Terumo, Japan) restored TIMI grade 2 flow into the distal LAD. Of note, during coronary balloon inflation the distal funnel of the aneurysm was exposed, with a calculated 20° angle between the intra- and extra-aneurysm portions of the balloon inside the LAD (Fig. 1B, C). At this point, as the patient's symptoms had resolved in the catheterization laboratory following successful balloon angioplasty and, given angiographic findings showing a large thrombus burden inside

the aneurysm, the treatment plan was to continue medical therapy followed by a re-look angiography 5–7 days later. Dual antiplatelet therapy (ASA and clopidogrel) was continued, in addition to anticoagulant therapy with IV unfractionated heparin. The patient remained stable on medical therapy in the Intensive Cardiac Care Unit, and underwent repeat coronary angiography 6 days after primary angioplasty demonstrating partial regression of the thrombus in a patent LAD with TIMI grade 3 flow (Fig. 1D–F). The maximal diameter of the aneurysm exceeded 15.0 mm associated with a sac length of 60 mm by intravascular ultrasound imaging. Based on the size, the aneurysm did not appear amenable to PCI with commercially available polytetrafluoroethylene (PTFE)-covered stents. Thus, in consultation with the Heart Team, a surgical approach combining aneurysm exclusion and coronary artery bypass grafting (CABG) was recommended. On day 21, the patient underwent an uncomplicated on-pump single vessel CABG with bypass of the LAD using the left internal mammary artery (LIMA). Intraprocedurally, the LAD coronary aneurysm (Fig. 1G, H) was released after transection of the pulmonary artery. The aneurysm was then opened and the proximal and the distal funnels were closed using a venous patch. Control coronary angiography revealed a total exclusion of the aneurysm (Fig. 1I) and good result of the LIMA bypass grafting (Fig. 1J). At 1-year follow-up, the patient remains asymptomatic with a stable ECG and LVEF of 38% assessed by cardiac magnetic resonance imaging.

In asymptomatic or stabilized patients with CAA thrombosis, several case reports have highlighted various successful conservative treatment strategies [2, 3]. At present, the role of direct oral anticoagulants for long-term treatment of CAA is currently unknown. Medically managed patients likely require lifelong therapy, as they are potentially at high risk for recurrent thrombosis should anti-thrombotic treatment be interrupted [2]. However, in patients presenting with STEMI, emergent PCI should be considered [4], optimally in the context of a Heart Team decision-making approach. Percutaneous exclusion of the CAA with one or many overlapped PTFE-covered stents may be of value in select patients with "short" aneurysms that are less than 10 mm in diameter located in straight, large proximal vessels [5, 6]. Furthermore, anatomical suitability should be considered carefully before covered stent use, as many of these devices require large, supportive guides and guidewires among other techniques to enhance delivery [7]. Recently, Boi et al. [8] reported a promising technique consisting of two different layers of overlapping stents named "double-layer bridging". Use of spirals to obtain aneurysm thrombosis is sometimes useful [9]. Patients presenting with CAA involving the left main coronary artery, bifurcation of significant side branch vessel lesions, multivessel coronary artery disease, giant aneurysms [10], or a separate indication for cardiothoracic surgery unrelated to CAA are usually referred for surgical revascularization. Although this case report does not correspond exactly to these criteria, the present Heart Team considered that surgical revascularization was the most appropriate strategy for favorable long-term outcome of the patient in the context of the large aneurysm dimensions, significant thrombus burden, and the high rate of target lesion revascularization associated with the use of a covered stent.

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