1955
UKS
CSS
UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA
www.uksrb.org

Časopis Udruženja kardiologa Srbije

SRCE i krvni sudovi

Heart and Blood Vessels

Journal of the Cardiology Society of Serbia

Dilemmas in management of pulmonary embolism
Dileme u dijagnostici i lečenju plućne embolije

New therapeutic options for reducing atherosclerotic cardiovascular disease residual risk

Chronic total occlusions: What's new?

Non-invasive testing in chronic coronary syndrome - comparison between functional and anatomic approach
Neinvazivni testovi u hroničnom koronarnom sindromu - poređenje funkcionalnog
i anatomskog pristupa

Telemedicine development in Serbian interventional cardiology
Razvoj telemedicine u Srpskoj interventnoj kardiologiji
Transradial versus transfemoral access for female patients who underwent primary PCI in STEMI:

Two years follow-up data from acute STEMI interventional registry

Ergospirometry in the assessment of functional significance of myocardial ischemia

Distal ulnar palmar approach to treat bifurcation stenosis of the left main (Medina 1.1.0) with Culotte technique

STEMI with high thrombus burden – two different therapeutic approaches?
STEMI sa velikim trombom – dva različita dijagnostička pristupa

Multivessel coronary artery disease – how to reach Heart Team's optimal decision
Višesudovna koronarna bolest – kako doneti naoptimalniji zaključak kardiohirurškog tima

Volumen 40 Broj 4
2021. godina

Ovaj broj sadrži radove prezentovanim na kongresu ZASINK 2021.
This issue contains manuscript presented at the ZASINK 2021

NOVINE U KARDIOLOGIJI

Agencija za lekove i medicinska sredstva Republike Srbije 14. aprila 2021. godine odobrila je upotrebu leka Forxiga® kod odraslih osoba za terapiju **simptomatske hronične srčane insuficijencije sa smanjenom ejekcionom frakcijom**.

FORXIGA® (dapagliflozin) Sažetak karakteristika leka, Predstavništvo AstraZeneca UK Ltd, Beograd, April 2021.

SAMO ZA STRUČNU JAVNOST

AstraZeneca

Predstavništvo AstraZeneca UK Limited Beograd
Milutina Milankovića 1i, Beograd - Novi Beograd,
11070 Novi Beograd
Tel: 011 3336 900 Fax: 011 3336 901

RS-1750,Maj 2021.

UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA

SRCE I KRVNI SUDOVI
HEART AND BLOOD VESSELS

Časopis izlazi redovno od 2011. godine i predstavlja nastavak časopisa Kardiologija (www.uksrb.rs)

Volumen 40 Broj 4 2021. godina

ADRESA UREDNIŠTVA
EDITORIAL OFFICE
Udruženje kardiologa Srbije
Višegradska 26, 11000 Beograd
Email: srceikrvnisudovi.urednistvo@gmail.com
www.uksrb.org

UPUTSTVO AUTORIMA

„Srce i krvni sudovi" je časopis Udruženja kardiologa Srbije koji objavljuje originalne radove, prikaze bolesnika, kardiovaskularne slike ("cardiovascular images"), pregledne i specijalne članke. Uz rukopis obavezno priložiti pismo koje su potpisali svi autori, a koje treba da sadrži:

- izjavu da rad prethodno nije publikovan i da nije istovremeno podnet za objavljivanje u nekom drugom časopisu,
- izjavu da su rukopis pročitali i odobrili svi autori.

Rukopis rada i sve priloge uz rad dostaviti elektronskim putem na adresu: sloba.d.obradovic@gmail.com, naslovljeno na: prof. dr Slobodan Obradović, glavni urednik časopisa „Srce i krvni sudovi". Prispele rukopise uređivački odbor šalje recenzentima radi stručne procene. Ukoliko recenzenti predlože izmene i dopune, tada se recenzirani rukopis dostavlja autorima s molbom da tražene izmene unesu u tekst ili pak u protivnom da argumentovano izraze svoje neslaganje sa datim primedbama recenzenta. Konačnu odluku o prihvatanju rada za štampu donosi glavni i odgovorni urednik zajedno sa uređivačkim odborom.
Za objavljene radove se ne isplaćuje honorar, a autorska prava se prenose na izdavača.
Časopis se štampa na srpskom jeziku, sa kratkim sadržajem prevedenim na engleski jezik. Inostrani autori mogu svoje članke, u celini, poslati na engleskom jeziku.
Molimo saradnike da svoje radove za časopis „Srce i krvni sudovi" pišu jasno, koncizno, racionalno, gramatički ispravno i u skladu sa sledećim uputstvima.

UPUTSTVA ZA PISANJE RADA

Tekst rada kucati u programu za obradu teksta Word, latinicom, fontom Times New Roman i veličinom slova 12 tačaka (12pt). Sve margine podesiti na 25 mm, veličinu strane na format A4, sa levim poravnanjem i uvlačenjem svakog pasusa za 10 mm. Ukoliko se u tekstu koriste specijalni znaci (simboli), koristiti font Symbol. Stranice numerisati redom u okviru donje margine desno, počev od naslovne strane. Podaci o korišćenoj literaturi u tekstu označavaju se arapskim brojevima u običnim zaokruženim zagradama, i to onim redosledom kojim se pojavljuju u tekstu. Rukopis rada dostaviti urađen po sledećem redosledu:

- naslovna strana,
- sažetak na srpskom jeziku,
- sažetak na engleskom jeziku, sa naslovom i institucijom odakle dolazi rad takođe na engleskom jeziku,
- tekst rada,
- tabele,
- opisi slika,
- posebno slike (grafikoni) ili fotografije.

Naslovna strana. Na posebnoj, prvoj stranici treba navesti sledeće:

- naslov rada bez skraćenica
- puna imena i prezimena autora (bez titula)
- kratak naslov rada
- zvaničan naziv i mesto ustanova u kojima autori rade: ukoliko su u radu autori iz različitih institucija, indeksirati autore iz raličitih institucija arapskim brojevima
- na dnu stranice navesti kontakt osobu, odnosno ime i prezime, adresu, broj telefona, faksa i e-mail adresu radi korespodencije

Kratak sadržaj na srpskom i engleskom jeziku. Na sledećoj strani priložiti kratak sažetak rada obima do 250 reči. Za originalne radove kratak sadržaj rada treba da sadrži: uvod, metod, rezultati i zaključak.
Prikazi bolesnika, pregledni i specijalni članci treba da imaju nestrukturisan sažetak obima do 150 reči.
Na kraju sažetka dostaviti i 2-4 ključne reči.
Svaki sažetak, sa naslovom i institucijom, mora biti preveden na engleski jezik.

Tekst rada. Tekst treba da sadrži sledeća poglavlja: uvod, metodi, rezultati, diskusija, zaključak, literatura. Svi podnaslovi se pišu malim slovima i boldovano. U radu koristiti kratke i jasne rečenice. Za nazive lekova koristiti isključivo njihova internacionalna nezaštićena imena. U radu se mogu koristiti određene skraćenice, ali samo kada je to neophodno. Za svaku skraćenicu koja se prvi put javlja u tekstu treba navesti i pun naziv. Sve rezultate navoditi u metričkom sistemu prema Međunarodnom sistemu jedinica (SI).
Originali rad ne treba da prelaze 4000 reči.
Prikaz bolesnika čine: uvod, prikaz bolesnika, diskusija, literatura. Prikaz bolesnika ne treba da prelazi 1500 reči.
Kardiovaskularne slike (cardiovascular images) ne treba da budu struktuirane i ne treba da prelaze 500 reči.
Pregledni i specijalni članci ne moraju da budu struktuirani po prethodnom modelu. Pregledni i specijalni članci ne treba da prelazi 5000 reči.

Literatura. Reference numerisati rednim arapskim brojevima prema redosledu navođenja u tekstu. Broj referenci ne bi trebalo da bude veći od 30, a broj citiranih originalnih radova mora da bude najmanje 80%. Izbegavati korišćenje apstrakta kao reference. Reference članaka koji su prihvaćeni za štampu označiti kao ,,u štampi" (in press) i priložiti dokaz o prihvatanju rada. Reference se citiraju prema Vankuverskim pravilima, koja su zasnovana na formatima koja koriste National Library of Medicine i Index Medicus. Naslove časopisa takođe treba skraćivati prema načinu koji koristi Index Medicus (ne stavljati tačke posle skraćenice).
Ukoliko rad koji se navodi ima više od 6 autora, onda navoditi tako što se posle trećeg autora staviti: et al. Stranice se citiraju tako što se navode početna i krajnja stranica (npr. 134-138).
Primer za navođenje reference iz časopisa: Leal J, Ramon Luengo-Fermnandes R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006;27:1610-1619.
Primer za navođenje reference iz knjige: Nichols A, Rourke MH. Aging and hypertension. U knjizi: Hypertension. Urednici: Nichols A, Rourke MH. Lea and Febiger; London/Melbourne, 1990:257-299.

Tabele se označavaju arapskim brojevima po redosledu navođenja u tekstu. Tabele raditi u programu Word, koristiti font Times New Roman, veličinu slova 12 pt, sa jednostrukim proredom i bez uvlačenja. Tabela mora da ima naslov i ukoliko se u tabeli koriste skraćenice, iste treba objasniti u legendi ispod tabele. Svaku tabelu dati na posebnom listu papira.

Slike (grafikoni) se označavaju arapskim brojevima po redosledu navođenja u tekstu. Na posebnom listu dati naslov sa opisom slika (grafikona) i ukoliko se koriste skraćenice, iste treba objasniti u nastavku. Svaki grafikon treba dati na posebnom listu papira. Slike (grafikone) dati u formatu ppt, ai ili eps.
Fotografije se označavaju arapskim brojevima po redosledu navođenja u tekstu. Primaju se isključivo originalne fotografije (crno-bele ili u boji) na sjajnom, glatkom (a ne mat) papiru. Na poleđini svake fotografije treba napisati redni broj. Fotografije moraju da budu u tif, eps ili ai formatu, najmanje rezolucije 300dpi.

Napomena. Rad koji ne ispunjava sve gore navedene tehničke uslove neće biti poslat na recenziju i biće vraćen autorima da ga dopune i isprave.
Glavni urednik i uređivački odbor zadržavaju pravo da radove, za koje smatraju da ne zadovoljavaju osnovne kvalitete i interesovanja publikovanja u časopisu, ne pošalju recenzentima i vrate autorima.

INSTRUCTIONS FOR AUTHORS

Heart and Blood Vessels is the official journal of the Serbian Cardiology Society and publishes Original articles, Case reports, Cardiovascular images, Review articles and Special articles. It is mandatory to enclose, along with the manuscript, a letter to the Editor-in-chief stating that the manuscript:

- has not been previously published or is currently submitted for review to another journal
- was read and approved by all authors

The manuscript with all appendices should be addressed to:
Prof. Slobodan Obradovic, MD, PhD
Editor-in-Chief, Heart and Blood Vessels
and mailed to sloba.d.obradovic@gmail.com

The Editorial Board will send it to reviewers for evaluation. Reviewers' comments will be forwarded to the author to either correct the original manuscript in accord with the suggestions or to express their opinion with adequate arguments in a letter to the Editor-in-chief explaining why they refrained from doing as reviewers deemed appropriate. The final decision will be made by the Editor-in-Chief together with the Editorial Board whether to accept the manuscript for publishing or not. For published manuscripts authors don't get fees, while copyright is transferred to the publisher. The journal is published in Serbian with summaries in English. Foreign authors can submit their manuscripts entirely in English.
We kindly request authors to keep their manuscripts for Heart and Blood Vessels clear, concise, rational, grammatically correct and in accord with the following instructions.

GENERAL INSTRUCTIONS

Manuscript text should be prepared using a Word processing package, in Times New Roman font size 12. All margins set at 25mm of an A4 page, with no alignment and 10mm tab at the beginning of each paragraph. In case special signs are used, please use Symbol font. Keep page numbering in the footer, starting from the Title page. References should be marked by order of appearance in the text in Arabic numerals in round brackets. The manuscript should be submitted in the following order:

- Title Page,
- Abstract,
- Body of the text,
- Tables, Figures' descriptions,
- Figures or photographs.

Title page. A separate, first page should encompass the following:

- the title
- the name(s) of authors,
- the institution(s) and location of all authors (Please, index in Arabic numerals the different Institutions by order of appearance),
- short title,
- at the bottom of the page cite the corresponding author with his contact address, phone, fax number and email address.

Abstract. Next page should contain a 250 words abstract. Original papers should encompass: Introduction, Methods, Results and Conclusion. Structured form of abstracts is not mandatory for case reports, review and special articles, but should not exceed 150 words.

The text should encompass: Introduction, Methods, Results, Discussion, Conclusions, and References. Subtitles should be typed in regular font and bold. Short and simple sentences are advised. For medication, it is recommended not to use trade names, but their generic names. Abbreviations can be used in the text, but only when necessary and properly introduced. All results should be cited in standard SI units.
An original paper should be up to 4000 words.
A Case Report consists of an Introduction, Case presentation, Discussion and References. A Case Report should be up to 1500 words. Cardiovascular Images shouldn't be structured and should be up to 500 words.
Review and Special Articles don't have to be structured and shouldn't exceed 5000 words.

References. References should be marked in order of appearance in Arabic numerals. The number of quoted references shouldn't exceed 50 out of which 80% should be original articles. It is advised to avoid abstracts as references. When quoting papers that are accepted for publishing, however, not yet published, mark them as in press and enclose a printed proof of the manuscripts' acceptance. References are quoted according to Vancouver style based on the formats used by National Library of Medicine and Index Medicus. Journals' titles should be shortened in accord with Index Medicus (no full stops after the abbreviation). If the paper quoted has over 6 authors, after the third one, et al. should be used Pages are quoted as first and last (i.e. 134-136).
Article citation example: Leal J, Ramon Luengo-Fermnandes R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J 2006;27:1610-1619.
Book citation example: Nichols A, Rourke MH. Aging and hypertension. In: Hypertension. Editors: Nichols A, Rourke MH. Lea and Febiger;London/Melbourne, 1990:257-299.

Tables are marked in order of appearance in Arabic numerals. Tables should be prepared using a Word processing package, Times New Roman font size 12, single spaced with no indent. Each Table should have a title. If abbreviations are used in the Table, they should be defined in the explanatory footnote below. Each table should be presented on a separate page.
Figures are marked in order of appearance in Arabic numerals. Please, provide on seprate page Figure legends. Each Figure should be prepared on a separate page using following format: ppt, ai or eps.
Photographs are marked in order of appearance in Arabic numerals. Only original photographs are accepted (black and white or color) on glossy paper. The back of each photograph should have the number and an arrow marking the top. The photograps should be prepared in following format: tip, eps, or ai, with minimal resolution of 300dpi.

Note. A paper not fully compliant with all aforementioned rules and regulations, will not be forwarded to reviewers, but returned to authors for correction. The Editor-in-Chief and the Editorial Board can reject any manuscript they deem not in the scope of the journal or not acceptable in terms of baseline quality of publishing material, even prior seeking reviewers' opinion.

CIP - Katalogizacija u publikaciji
Narodna biblioteka Srbije, Beograd

Srce i krvni sudovi: Časopis Udruženja kardiologa Srbije
Heart and blood vessels: Journal of Cardiology society of Serbia
Editor in-chief Slobodan Obradović, Godina 11,
Volumen 40, Broj 4
Beograd, Višegradska 26: Udruženje kardiologa Srbije
2021-Beograd: Newassist doo
Tromesečno-Broj 1 izašao 2011. god.

ISSN 182-4835=Srce i krvni sudovi
COBISS.SR-ID 174253580

1955 UKS CSS
UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA

SRCE I KRVNI SUDOVI
HEART AND BLOOD VESSELS

Volumen 40 Broj 4 2021. godina

Sadržaj / *Content*

Dilemmas in management of pulmonary embolism **247**
Dileme u dijagnostici i lečenju plučne embolije
Slonodan Obradovic, Boris Dzudovic, Stavros Konstantinides

New therapeutic options for reducing atherosclerotic cardiovascular disease residual risk **251**
Nathan D. Wong

Chronic total occlusions: What's new? **257**
Aleksandr Osiev, Vladimir Mitov, Egor Malakhov

Non-invasive testing in chronic coronary syndrome - comparison between functional and anatomic approach **261**
Neinvazivni testovi u hroničnom koronarnom sindromu - poređenje funkcionalnog i anatomskog pristupa
Vojislav Giga, Nikola Bošković, Ana Đorđević-Dikić, Ivana Nedeljković, Branko Beleslin

Telemedicine development in Serbian interventional cardiology **264**
Razvoj telemedicine u Srpskoj interventnoj kardiologiji
Aleksandar Jolić, Milan Nikolić, Vladimir Mitov, Dragana Adamović, Marko Dimitrijević, Milan Nedeljković

Transradial versus transfemoral access for female patients who underwent primary PCI in STEMI: Two years follow-up data from acute STEMI interventional registry **268**
Oliver Kalpak, Hristo Pejkov

Ergospirometry in the assessment of functional significance of myocardial ischemia **274**
Ivana Nedeljkovic, Vojislav Giga, Ana Djordjevic Dikic, Nikola Bošković, Milorad Tešić, Milan Dobrić, Marina Ostojic, Milan Nedeljković, Marko Banović, Olga Petrovic, Ivana Jovanović, Branko Beleslin

Distal ulnar palmar approach to treat bifurcation stenosis of the left main (Medina 1.1.0) with Culotte technique **277**
Oktaj Maksudov, Farhat Fouladvand

STEMI with high thrombus burden – two different therapeutic approaches? **282**
STEMI sa velikim trombom – dva različita dijagnostička pristupa
Vladimir Zdravković, Đorđe Stevanović

Multivessel coronary artery disease – how to reach Heart Team's optimal decision **286**
Višesudovna koronarna bolest – kako doneti naoptimalniji zaključak kardiohirurškog tima
Ivan Ilic, Dragan Topic

Srce i krvni sudovi 2021; 40(4): 247-250

Review article

Dilemmas in management of pulmonary embolism

Slonodan Obradovic[1,2], Boris Dzudovic[3], Stavros Konstantinides[4,5]

[1]Clinic of Cardiology, Military Medical Academy, Belgrade, [2]School of Medicine, University of Defense, Belgrade, [3]Clinic of Emergency Internal Medicine, Military Medical Academy, Belgrade, [4]Center for Thrombosis and Hemostasis, Johannes Gutenberg University Mainz, Germany, [5]Department of Cardiology, Democritus University of Thrace, Greece

Abstract **Background.** Acute pulmonary embolism (PE) is very heterogeneous disease regarding etiology and clinical presentation. Because of that the treatment of PE need multidisciplinary approach creating locally pulmonary embolism response teams (PERT) to deal with various problems associated with PE management.

Review. We try to review some unresolved issues in the management of PE, through the diagnostic, reperfusion, anticoagulation and subgroups treatments. In spite of the recent advancement in oral anticoagulation therapy for venous thromboembolism, risk stratification and diagnosis of chronic thromboembolic pulmonary hypertension, all build in the 2019 European Society of Cardiology guidelines, many important obstacles in PE treatment remained. Unlike acute coronary syndrome, PE field is lacking randomized clinical trials and many important questions are opened in front of everyday practice.

Conclusion. There are many unmet needs in PE management and we need a lot of randomized trials or data from large registries to resolve some burning problems in the handling of PE patients.

Key words Pulmonary embolism, reperfusion, anticoagulation therapy, biomarkers

Introduction

Acute pulmonary embolism (PE) is the third cause of cardiovascular death, behind the acute myocardial infarction and stroke[1]. The annual incidence of acute PE is approximately 100 per 100.000 inhabitants with significant dependents on age. During the severe acute respiratory syndrome coronavirus (SARS-CoV)-2 pandemic, the incidence of PE is probably doubled, since 5% of COVID-19 PCR positive patients who are examined in emergency departments[2] may have PE. Taking these data into account, approximately 7000 patients would have acute PE in Serbia each year. Intra-hospital case-fatality rate of PE is around 10%, and it can be estimated that 500-700 patients die directly from PE every year in Serbia. Apart of this, acute PE is a leading cause of death in pregnancy and the second cause of death in patients with malignant disease. Many hereditary and phenotypic factors can influence the occurrence of PE and we can call PE as a shadow of various diseases and conditions.

Diagnostic dilemmas

Patients in cardio-respiratory arrest. An algorithm for diagnosis acute PE in patients admitted to the hospital under cardiopulmonary resuscitation (CPR) does not exist. Definitely, acute PE is a differential diagnosis. The data of bystanders could be of great value, because acute dyspnea could precede the cardiac arrest and if there are any data about the potential risk factors for PE (recent surgery, trauma or other illness, hospitalization, previous PE, thrombophilia, long journey, use of certain drugs etc.) we will have strong suspicious for acute PE as a cause of cardiac arrest. The signs of deep vein thrombosis also contribute to this conclusion. Bedside echocardiography is the most useful diagnostic tool under these circumstances, where right ventricle dysfunction could be observed in severe acute PE[3]. However, some other diseases also can provoke acute right ventricle dysfunction, or chronic pulmonary hypertension could also make the diagnosis of acute PE difficult. Additionally, if we find trias, acute dyspnea before loss of consciousness, signs of deep vein thrombosis and right ventricle dysfunction on cardiac ultrasound, the diagnosis of acute PE is very probable and we can proceed to reperfusion therapy if patient is hemodynamically stabilized[4]. Bolus of 50 mg tPA can be repeated twice during CPR[4]. Treatment with thrombolysis during resuscitation has resulted to better survival in case-series[5].

Diagnosis of high-risk PE. Current PE ESC guidelines recommend cardiac ultrasound as the first line diagnostic tool in patient with suspected high-risk PE. However, in patients with suspected high-risk acute PE, with hypotension, echocardiography examination at admission may not be sufficient to make a decision for applying thrombolytic therapy, if the thrombus not seen in right heart chambers, or if patient doesn't have clear signs of deep vein thrombosis[6]. Some patients also can be in a very serious condition, or have very fast tachycardia or poor

Corresponding author: Slobodan Obradovic MD PhD, professor of Cardiology, Clinic of Cardiology, Military Medical Academy, School of Medicine, University of Defense, Belgrade, Serbia, e-mail: sloba.d.obradovic@gmail.com

echocardiography windows, which preclude qualitative ultrasound examination. Computed tomography pulmonary angiography (CTPA) should be performed before the decision for reperfusion therapy whenever is possible.

The role of the lower limb venous compression ultrasound examination (CUS). The significance of CUS of lower limbs veins in PE patients with symptoms suggestive of DVT is controversial. What clinical decision we should make according to this finding? Early hospital discharge is recommended without the necessity for CUS using European Society of Cardiology (ESC) risk model and cardiac ultrasound. Recently published HOT-PE study used HESTIA criteria and cardiac ultrasound, and not CUS for the discrimination of low-risk PE patients planned for the early hospital discharge[7].

Looking for malignancy. How deep we should be looking for malignant disease in patient with acute PE without visible reason for that? During CTPA, it should be wise to examine the abdomen, at least upper abdomen and to carefully explore lungs, mediastinum, liver, kidneys, pancreas, spleen and suprarenal glands. We may also determine also determine some tumor markers if deemed necessary, and perform a gynecological examination, mammography or breast ultrasound, and thyroid examination. Rarely, a malignant process may be found and treated before dissemination, but in most cases cancer is already evident and advanced at diagnosis of acute PE. Therefore, rather limited malignancy survey and follow-up of the patients are needed[8].

Looking for thrombophilia. To look or not to look hereditary thrombophilia? Although it usually does not change the dose or duration of anticoagulant treatment for the patient herself/himself[9] we look for hereditary thrombophilia in patients younger than 50 years especially in females because of the possible complications related to pregnancy[10]. It may also be wise to make an effort to diagnose or exclude antiphospholipid syndrome[11], especially in younger patients without clear risk factors for PE.

Cardiac troponin as a marker of higher PE risk. Use of cardiac troponin for the risk stratification in acute PE has some caveats. Cardiac troponin as a marker of cardiac injury can increase in various reasons such as hypoxemia, coronary disease, tachycardia, anemia etc. Especially high-sensitive troponin can be elevated in healthy elderly patients with concomitant renal dysfunction[12]. Therefore, cardiac troponin may be non-specific for the cause of cardiac injury and for the hemodynamic changes in seen in severe PE. The use of troponin as a marker for high-intermediate PE could make a bias toward older patients with higher risk for bleeding. The cut-off value above the 99-percentiles of the normal laboratory range is too low for the risk stratification in PE. However, only cardiac troponin was used in the large randomized PEITHO trial[13] and recognized as the laboratory marker of choice for risk stratification in the 2019 ESC PE guidelines.

Treatment of high-risk acute PE

Reperfusion. Patients with high-risk PE are hemodynamically compromised or in cardiac arrest. They need prompt reperfusion therapy and resuscitation measures such as mechanical ventilation or extra-corporal-membrane oxygenation (ECMO) and inotrope stimulation with norepinephrine[3]. However, recent data has demonstrated that about only 20% of high-risk PE patients has been treated with reperfusion therapy in USA and Germany[14,15]. The high risk for bleeding and severe comorbidities preclude the wider application of thrombolytic therapy in this group of patients. The clinical benefits of surgical embolectomy and catheter-directed therapy have not been tested in randomized trials and the data of their use are limited to case series and reports with strong possibility of bias through the the selection of patients for certain procedures. It is obvious that many patients with high-risk PE are not eligible for the systemic thrombolysis which is the most available treatment option for reperfusion. All other reperfusion therapies need a high degree of expertise and there is a significant learning curve for the different surgical or catheter based procedures.

Treatment of patient in cardiac arrest. Several systemic thrombolytic protocols are approved by ESC. However, none of them are suitable for patient in cardiac arrest, during resuscitation. Tenecteplase, the bolus thrombolysis, is not recommended because of the high bleeding risk of that drug demonstrated in PEITHO study[13]. Other thrombolytic protocols need time. British Thoracic Society Standards of Care Committie Pulmonary Embolism Guideline Development Group guidelines recommended bolus of 50 mg of tPA (or double dose) in this circumstance and that is the most used protocol of thrombolytic therapy during resuscitation in PE patients in the literature[16,17].

Treatment of intermediate-high risk PE

Mortality rate from PE is discrepant between randomized trials and observational studies. In the randomized PEITHO trial[13], intra-hospital mortality was less than 2% in both the thrombolytic and placebo (only anticoagulation) arm. In contrast, in several other trials, in this group of patients' early mortality rate was 5-15%[18,19]. Many experts agree that this group of patients also needs reperfusion therapy, but standard systemic thrombolytic protocols have an unfavorable net effect, with the benefit in prevention of hemodynamic instability offset by the high risk for major bleeding. Catheter directed thrombolysis or mechanical thrombectomy are promising treatment modalities in this group of patients which use a low dose of tPA[20] or only mechanical fragmentation and aspiration of thrombi without thrombolytic therapy[21]. There is currently a gap between clinical practice and guidelines, with an increasing number of centers performing almost routinely catheter-directed therapy in intermediate-high- and high-risk PE patients without supporting evidence from randomized trials.

There are several studies in which reduced, usually a half of the systemic tPA dose was used with doubtful signs of benefit considering the balance between efficacy and safety[22,23]. There is also (only) one small randomized study that compared systemic half-dose tPA with full dose t-PA in high-risk PE[24]. Additionally, comparison of half-dose tPA with low-molecular heparin in patients with intermedi-

ate-high risk PE was not done in a randomized fashion. The largest observational, retrospective trial[22] did not confirm that half-dose tPA was better than full-dose tPA in reducing mortality or bleeding.

How to estimate anticoagulation failure and to aggravate the therapy? Current guidelines recommend close hemodynamic monitoring in patients with intermediate-high PE for at least 48 hours and the use of rescue thrombolytic therapy, or some other reperfusion therapy in case of hemodynamic decompensation[3]. However, if we wait for shock to develop, it may be too late for successful reperfusion therapy. Earlier, sensitive markers of deterioration should be used, such as increase of heart rate, worsening of hypoxemia, fall of systolic blood pressure, but not below the 90 mmHg, increase of blood lactate concentration, or worsening the RV performance on cardiac ultrasound[21]. Some authors also recommended that an unchanged status after 48 hours of anticoagulation therapy means treatment failure and that we should then proceed to reperfusion modalities[21].

When to start a direct oral anticoagulant in patients with severe PE?
It is obvious that it is not prudent to start direct oral anticoagulants (DOAC) as the first line anticoagulation in patients with intermediate-high and high-risk PE because escalation therapy to systemic or local thrombolysis may become necessary[25]. The combination of DOAC and thrombolysis is unknown zone and it should be avoided if possible. The use of thrombolytic therapy (the authors advise a reduced dose of tPA) in patients on DOAC who develop high-risk PE can be an option if there is no possibility to use catheter-based mechanical thrombectomy. DOACs should be initiated as soon as hemodynamic stabilization is achieved[25].

How to choose DOAC?
Four DOAC have had large published randomized trials in patients with venous thromboembolism which in summary showed that they are non-inferior to vitamin K antagonists for the prevention of recurrent VTE events and safer regarding the occurrence of major or clinically relevant non-major bleeding, in particulare causing significantly less intracranial bleeding than vitamin K antagonists[3]. DOACs are also more convenient for use compared to vitamin K antagonists. All these facts to the recommendation of guidelines by international scientific societies to recommend DOACs in preference to a vitamin K antagonist[3]. Rivaroxaban has a higher initial dose, 15 mg bid for 3 weeks, following by once daily dosing of 20 mg per day. For apixaban, the initial dose is 10 mg bid for 7 days followed by 5 mg bid thereafter. Both rivaroxaban and apixaban have robust data from the randomized trials for the extension therapy after the first the six months following an index VTE event, where the lower dose of rivaroxaban (10 mg per day) and apixaban (2.5 mg bid) were effictive and safe for the prevention of VTE for the long-term anticoagulation. We can choose the higher dose of rivaroxaban or apixaban or the lower doses of these drugs depending on the risk for VTE recurrence and hemorrhagic risk[3]. On the other hand, dabigatran has been tested after at least five days of heparin therapy in higher dose of 150 mg bid. Dabigatran was also non-inferior to a enoxaparin/vitamin K antagonists and similarly safe. Lower doses of dabigatran have not been tested for extended anticoagulation. Dabigatran is contraindicated in patients with glomerular filtration rate (GFR) less than 50 ml/min. Both rivaroxaban and apixaban can be used in this indication without dose reduction in patients with GFR>15 ml/min[3].

Can we safely discharge patient with low-risk PE early?
New anti Xa drugs, rivaroxaban and apixaban can be used from the start as anticoagulant therapy in patients with PE. This enables early discharge from the hospital of patients with low-risk PE. Recent trials successfully tested this using HESTIA criteria and simplified PESI score for the selection of patients with lowest PE risk who could be safely treated at home[7,26]. Patients without any of the HESTIA criteria and those who are PESI 0 can be safely treated at home using rivaroxaban or probably apixaban if they have good social support and easy contact with the physician who treated PE. In this circumstances it is important to exclude serious comorbidities, PE recurrence risk and hemorrhagic risk. Cardiac ultrasound may be necessary for the decision.

How to treat symptomatic patients in sub-acute phase of PE?
A small percentage of patients have persisting symptoms, mostly dyspnea on effort and fatigue, in the subacute phase of PE[27]. These can be accompanied by pulmonary hypertension and RV dysfunction. Cardiac ultrasound, 6-minute walking test, multi-slice detector computed pulmonary angiography, BNP and right heart catheterization is needed before treatment of these patients. Some of them may benefit from sugical pulmonary endarterectomy, percutaneous balloon pulmonary angioplasty or early treatment with drugs for pulmonary hypertension.

Unmet needs in the management of cancer associated thrombosis
There are many unresolved issues in the management of cancer associated thrombosis (CAT). CAT maybe related to tumor and patient characteristics, to surgical, radiation and medicament therapy. VTE associated with *currative* oncology surgery may have very low risk for recurrence and it is very important to manage carefully at follow-up the malignant disease activity after surgery[28]. On the other side, metastatic or advanced local diseases, especially adenocarcinomas may have prolonged thrombotic storm which is resistant to anticoagulant therapy and lead to death. Anti Xa direct oral anticoagulants are at least as (if not more) effective and similarly safe as low molecular weight heparins in patients with active cancer-associated thrombosis[29]. Idiosyncracy on thrombotic reaction to some oncologic drugs is also very often present[30]. Various tumors have very different pathophysiology mechanisms of prothrombotic state. Therefore, we need tumor specific randomized trials for CAT management.

References

1. Belohlavek J, Dytrych V, Linhart A. Pulmonary embolism, part I: epidemiology, risk factors and risk stratification, pathophysiology, clinical presentation, diagnosis and nonthrombotic pulmonary embolism. Exp clin cardiol 2013;18(2):129-38.
2. Miro O, Jimenez S, Mebazzaa A, et al. Pulmonary embolism in patients with COVID-19. Eur Heart J 2021;33:3127-42.
3. Konstatinides SV, Meyer G, Becattini C, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). Eur Heart J 2020;41(4):543-603.
4. Kurckyian I, Meron G, Sterz F, et al. Pulmonary embolism as cause of cardiac arrest. Arch Intern Med 2000;160:1529-35.
5. Thrombolysis during resuscitation for out-of-hospital cardiac arrest caused by pulmonary embolism increases 30-day survival: findings from the French national cardiac arrest registry. Chest 2019;156:1167-75.
6. Harjola V-P, Mebazza A, Celutkiene J, et al. Contemporary management of acute right ventricular failure: a statement from the Heart Failure Association and Working Group on Pulmonary Circulation and Right Ventricular Function of the European Society of Cardiology. Eur J Heart Fail 2016;18:226-41.
7. Barco S, Schimdtmann I, Ageno W, et al. Early discharge and home treatment of patients with low-risk pulmonary embolism with oral factor Xa inhibitor rivaroxaban: an international multicenter single-arm clinical trial. Eur Heart J 2020;41:509-18.
8. Van Es N, Le Gal G, Martin-Oten H, et al. Screening for occult cancer in patients with unprovoked venous thromboembolism: a systematic review and meta-analysis of individual patient data. Ann Intern Med 2017;167:410-7.
9. Stern RM, Al-Samkari, Connors JM, Thrombophilia evaluation in pulmonary embolism. Curr Opin Cardiol 2019;34:603-9.
10. Robertson L, Wu O, Langhorne P, et al. Thrombophilia in pregnancy: systematic review. Br J Haemetol 2006;132:171-96.
11. Kelling D, Mackie I, Moore GW, Greer IA, Geaves M. Guidelines on the investigation and management of antiphospholipid syndrome. Br J Haematol 2012;157:47-58.
12. Giannitsis E, Katus HA. Biomarkers for clinical decision-making in the management of pulmonary embolism. Clin Chem 2017; 63(1):91-100.
13. Meyer G, Vicaut E, Danays T, et al. Fibrinolysis in patients with intermediate-risk pulmonary embolism. N Engl J Med 2014; 370:1402-11.
14. Stein PD, Matta F, Hughes PPG, Hughes JM. Nineteen-year trends in mortality of patien hospitalized in the United States with high-risk pulmonary embolism. Am J Med 2021 (in press).
15. Keller K, Hobhom M, Ebner M, et al. Trends in thrombolytic treatment and outcomes of acute pulmonary embolism in Germany. Eur Heart J 2020;41:522-9.
16. British Thoracic Society Standards of Care Commitie Pulmonary Embolism Guideline Development GroupThorax 2003;58:470-83.
17. Double bolus alteplase therapy during cardiopulmonary resuscitation for cardiac arrest due to massive pulmonary embolism guided by focused bedside echocardiography. Case Reports in Critical Care 2018; article ID 7986087:1-7.
18. Becattini C, Agnelli G, Lankeit M, et al. Acute pulmonary embolism: mortality prediction by the 2014 European Society of Cardiology risk stratification model. Eur Resp J 2016;48:780-6.
19. Tong CR, Zhang ZH. Evaluation factors of pulmonary embolism severity and prognosis. Clin Appl Thromb Hemost 2015;21:2773-84.
20. Tapson VF, Sterling K, Jones N, et al. A randomized trial of the optimum duration of acoustic pulse thrombolysis procedure in acute intermediate-risk pulmonary embolism: the OPTALYSE PE Trial. JACC Interv 2018;11:1401-10.
21. Pruszczyk P, Federikus A, Kucher N, et al. Percutaneous treatment options for acute pulmonary embolism: a consensus paper of the ESC Working Group on Pulmonary Circulation and Right Ventricular Function and European Association of Percutaneous Cardiovascular Interventions. Eurointervention 2022 (in press).
22. Kiser TH, Burnham EL, Clark B, et al. Half-dose versus full dose algteplase for treatment of pulmonary embolism. Crit care Med 2018;46:1617-25.
23. Brandt K, McGinn K, Quedado J. Low-dose systemic alteplase (tPA) for the treatment of pulmonary embolism. Ann Pharmacother 2015;49:818-24.
24. Wang C, Cheng X, Weng X, et al. Efficacy and safety of low dose recombinant tissue-type plasminogen activator for the treatment of acute pulmonary embolism: a randomized, multicenter, controlled trial. Chest 2010;137:254-62.
25. Leentjens J, Peters M, Kramers C. Initial anticoagulation in patients with pulmonary embolism: thrombolysis, unfractionated heparin, LMWH, fondaparinux, or DOACs? Br J Clin Pharm 2017;83:2356-66.
26. Triaging acute pulmonaryembolism for home treatment by Hestia or simplified PESI criteria: the HOME-PE randomized trial. Eur Heart J 2021;42:3146-57.
27. Fernandes T, Planquette B, Sanchez O, Morris T. From acute to chronic thromboembolic disease. Ann Am Thoracic Soc 2016;13(suppl 3):S207-14.
28. Kim AS, Khorana AA, McCrae KR. Mechanisms and biomarkers of cancer-associated thrombosis. Trans Res 2020;225:33-53.
29. Li A, Garcia DA, Lyman GH, Carrier M. Direct oral anticoagulant (DOAC) versus low-molecular-weight heparin (LMWH) for treatment of cancer associated thrombosis (CAT): A systematic review and meta-analysis. Thromb Res 2019;173:158-163.
30. Steven P. Grover SP, Hisada YM, Kasthuri RS, Reeves BN, Mackman N. Cancer therapy–associated thrombosis. Arterioscler Thromb Vasc Biol 2021;41:1291–305.

Sažetak

Dileme u dijagnostici i lečenju plućne embolije

Slonodan Obradović[1,2], Boris Džudović[3], Stavros Konstantinides[4,5]

[1]Klinika za kardiologiju, Vojno medicinska akademija, Beograd, [2]Medicinski fakultet, Univerzitet odbrane, Beograd, [3]Klinika za urgentnu intrenu medicinu, Vojno medicinska akademija, Beograd, [4]Centar za trombitu I hemostazu, Johannes Gutenberg Univerzitet Mainz, Nemačka, [5]Odeljenje kardiologije, Democritus Univerzitet Trakije, Grčka

Uvod. *Akutna plućna embolija (PE) je veoma heterogeno oboljenje u odnosu na etiologiju i kliničku prezentaciju. Zbog toga tretman PE iziskuje multidisciplinarni pristup i stvaranje lokalnih timova za lečenje PE koji će se uhvatiti u koštac sa raznim problemima u tretmanu PE.*

Pregledni rad. *Pokušali smo da prikažemo problem u današnjem tretmanu PE, kroz dijagnostiku, reperfuziju, antikoagulantnu terapiju i lečenje određenih podgrupa bolesnika. I pored skorašnjeg napretka u lečenju bolesnika sa PE, kao što su uvođenje direktnih oralnih antikoagulantnih lekova, bolje stratifikacije rizika PE i uvrštavanja algoritma za dijagnostiku hronične tromboembolijske bolesti pluća u preporuke za tretman PE iz 2019-te godine, mnogo prepreka u lečenju je ostalo. Suprotno od akutnog koronarnog sindroma, u oblasti PE nedostaju randomizovane studije i mnoga važna pitanja su otvorena u svakodnevnoj praksi.*

Zaključak. *Postoji mnogo važnih, nerešenih pitanja u vezi dijagnostike i lečenja PE, i potrebne su nam brojne randomizovane studije i podaci iz velikih registara da bi bolje lečili PE pacijente.*

Ključne reči: *plućna embolija, reperfuzija, antikoagulantna terapija, biomarkeri*

Srce i krvni sudovi 2021; 40(4): 251-256

Review article

New therapeutic options for reducing atherosclerotic cardiovascular disease residual risk

Nathan D. Wong

Heart Disease Prevention Program, Division of Cardiology, University of California, Irvine, USA

Abstract Adults with atherosclerotic cardiovascular disease (ASCVD) bear a significant risk of recurrent ASCVD events, particularly those classified as very high risk, despite current standard-of-care therapies. While addressing lifestyle modification efforts to reduce this "residual risk" must remain the foundation of ASCVD risk reduction efforts, there is significant interest in the development of newer therapies that may provide further benefit. Important domains for targeting therapies include those directed at lipid, inflammatory, metabolic, and thrombotic residual risk. With respect to therapies addressing lipid targets, ezetimibe and PCSK9 monoclonal antibody therapies have been shown to reduce ASCVD risk beyond statin therapy. Inclisiran, currently approved in the European Union, also lowers LDL-C, with cardiovascular outcome data pending as to whether it will provide further ASCVD risk reduction. Further, therapies to lower lipoprotein(a) are in development that hold promise for reducing lipoprotein(a)-associated residual risk. Also, of interest has been whether targeting inflammation will reduce ASCVD risk. While canakinumab did demonstrate proof of concept in being the first such therapy to selectively reduce inflammation resulting in ASCVD event reduction, cost and fatal infections precluded its further development. Moreover, clinical trials of colchicine have also shown benefit, but recommendations are yet to adopt this as a therapeutic option to reduce ASCVD risk. Metabolic agents include icosapent ethyl, SGLT2 inhibitors, and GLP1 receptor agonists that now have evidence for reducing cardiovascular outcomes. Finally, in high risk individuals, antithrombotic therapy with rivaroxiban or dual antiplatelet agents have shown benefit. The potential remains great for the development and use of newer therapies to address residual ASCVD risk.

Key words atherosclerotic cardiovascular disease, residual risk, dyslipidema, inflammation, thrombosis, metabolic

Persons with atherosclerotic cardiovascular disease (ASCVD), including history of acute coronary syndrome, myocardial infarction, ischemic stroke, or peripheral arterial disease, remain at substantial risk of recurrent events and mortality despite evidence-based standard of care therapies, a concept known as "residual risk". In the Atherothrombosis in Metabolic Syndrome and with Low HDL/High Triglycerides: Impact on Global Health Outcomes (Aim-HIGH) cohort of more than 3000 subjects with prior ASCVD, overall 16% of subjects, despite on statin therapy, suffered a recurrent ASCVD event over a mean follow-up of 4.2 years, translating into an annual event rate of approximately 4%1. The best predictors of residual risk in these statin-treated subjects with ASCVD included, male sex, hemoglobin A1c, alcohol use (inversely), family history of cardiovascular disease, homocysteine, history of carotid artery disease, and lipoprotein(a). A more recent analysis of the Marketscan database of over 27,000 adults with prior ASCVD[2] showed 1539 recurrent ASCVD events (5.7%) to occur over a median follow-up of 2 years. Over half (53%) of such ASCVD patients were classified as "very high risk" and had event rates 3-fold greater than those not at very high risk (53.1 vs. 17.0 per 1,000 person years), and of those who were very high risk with a history of multiple major ASCVD conditions (26% of those classified as very high risk), recurrent ASCVD event rates were even higher (89.8 per 1,000 person years). Current US guidelines[3] classify those with prior ASCVD as very high risk if they have multiple major ASCVD conditions (recent acute coronary syndrome, myocardial infarction, ischemic stroke, or symptomatic peripheral arterial disease) or one such major event and multiple high risk conditions (such as age 65 years or greater, diabetes, cigarette smoking, chronic kidney disease, or hypertension). It has been suggested that multiple cardioprotective standard of care therapies, including statins, beta blockers, ACE inhibitors / angiotensin receptor blockers, and aspirin, if given together, can reduce ASCVD risk by as much as 75%[4,5]. Of interest, while recent trials of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have provided statistically significant reductions in ASCVD outcomes beyond statin therapy, the absolute risk reductions are modest—1.5% in the Fourier trial[6] involving evolocumab and 1.6% in Odyssey Outcomes[7] involving alirocumab, with still nearly 10% of patients in these trials suffering recurrent ASCVD events despite treatment with a PCSK9 inhibitor.

Correspondence to: N.D. Wong (ndwong@uci.edu), C240 Medical Sciences, University of California, Irvine, CA, USA 92697.

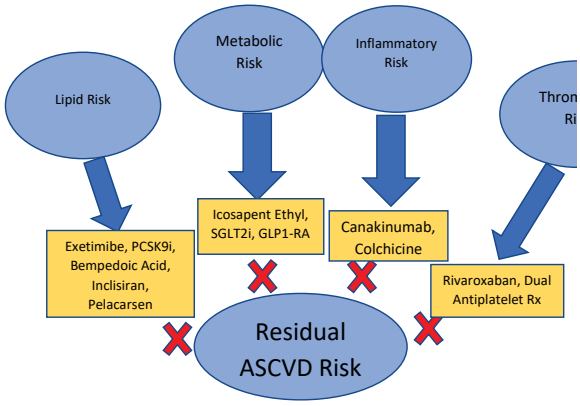


Figure 1. Domains for targeting atherosclerotic residual cardiovascular disease risk

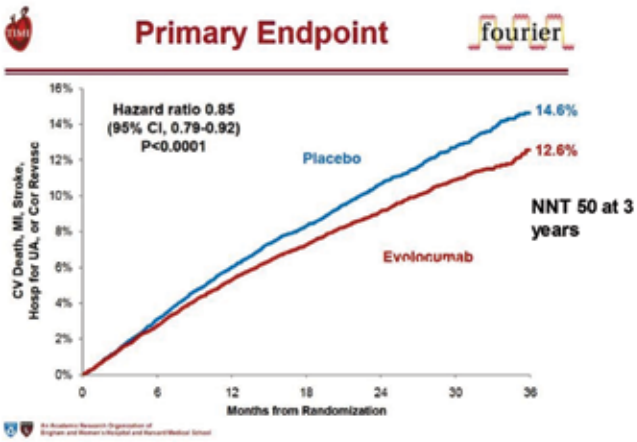
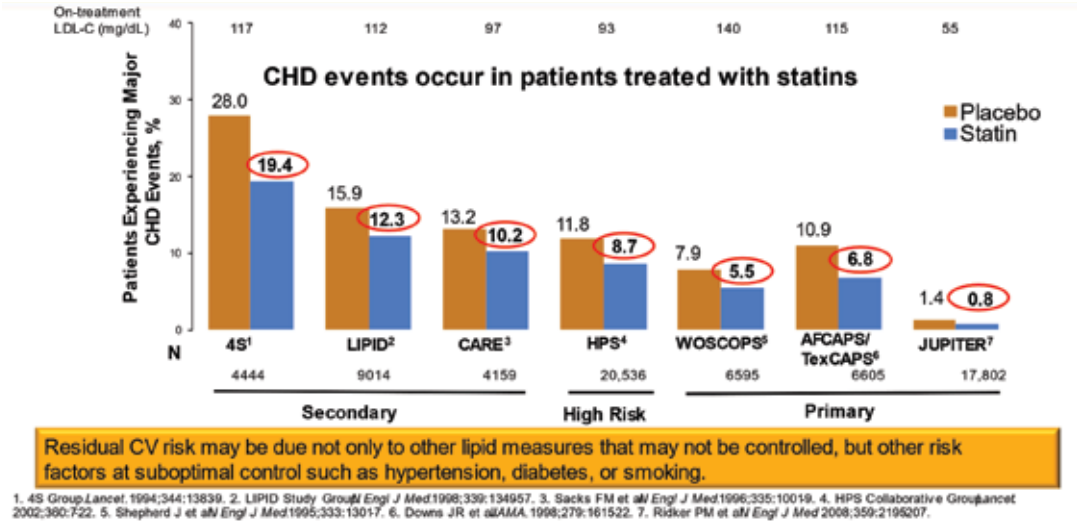


Figure 3. Evolocumab provides further 15% ASCVD reduction beyond statin therapy in FOURIER trial (from Sabatine et al.)



1. 4S Group.*Lancet*.1994;344:13839. 2. LIPID Study Group*N Engl J Med*1998;339:134957. 3. Sacks FM et al*N Engl J Med*1996;335:10019. 4. HPS Collaborative Group*Lancet* 2002;360:7122. 5. Shepherd J et al*N Engl J Med*1995;333:13017. 6. Downs JR et al*JAMA*.1998;279:161522. 7. Ridker PM et al*N Engl J Med* 2008;359:2195207.

Figure 2. Despite ASCVD benefit with statin monotherapy, substanial residual cv risk remains

At the foundation of addressing ASCVD residual risk is to address lifestyle-related factors that may help explain such risk. Besides complete smoking cessation and avoidance of environmental tobacco smoke, recent lifestyle management guidelines recommend consuming a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; includes low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils and nuts; and limits intake of sweets, sugar-sweetened beverages, and red meats along with at least moderate intensity physical activity of 150 minutes (or 75 minutes vigorous activity) per week, along with recommendations for resistance training[8].

This report reviews newer and emerging therapeutic targets that are focused on addressing residual ASCVD risk. We will focus on four domains for targeting therapies: those directed at lipid, inflammatory, metabolic, and thrombotic residual risk (Figure 1).

Therapies for Lipid Residual Risk

Over the past 3 decades, a wealth of primary and secondary prevention clinical trials of statin therapy have demonstrated overall 25-40% reductions in the risk of ASCVD events[9], establishing them as the standard of care for patients with known ASCVD as well as those at higher risk of ASCVD according to recent guidelines[3]. However, significant "residual risk" remains (Figure 2). To address remaining "lipid" residual risk, there has been significant interest and exploration into non-statin therapies, including niacin and fibrates, cholesterol absorption inhibitors (ezetimibe), PCSK9 inhibitors, and more recent novel therapies such as silencing RNA (siRNA) therapies for low density lipoprotein-cholesterol and antisense oligonucleotide therapy for lipoprotein(a). Large-scale clinical trials of niacin[10,11] and cholesterol ester transferase protein (CETP) inhibitors[12] have largely been negative or with limited clinical benefit, resulting in a failure to prove the high density lipoprotein-cholesterol (HDL-C) hypothesis. Moreover, major trials of fibrate therapy[13] have also failed their primary endpoints, although we await the results of the PROMINENT trial involving pemafibrate due out within a few years[14].

The IMPROVE-IT trial[15] was the first landmark non-statin trial to demonstrate benefit, in this case with ezetimibe, a cholesterol absorption inhibitor, although the benefit demonstrated (on top of a background of 40 mg simvastatin therapy) was modest, with a relative risk reduction of only 6%. But given the high-risk population studied (acute coronary syndrome within 10 days) and the

long 7-year duration of the trial, there was a 2% absolute risk reduction resulting in a number needed to treat of 50. Ezetimibe therapy has thus been integrated into treatment of high risk persons beyond statin therapy by most national guidelines.

More recently, the FOURIER[6] and Odyssey Outcomes[7] trials of PCSK9 inhibitors further demonstrated improvement in cardiovascular outcomes beyond statin therapy (including some patients on ezetimibe), both showing a 15% relative risk reduction. FOURIER included a wide range of mostly stable ASCVD patients (Figure 3) while ODYSSEY OUTCOMES included persons within one year of their acute coronary syndrome. However, despite powerful PCSK9 therapy that lowers LDL-C 50-60% beyond statin therapy, 9.8% of patients in FOURIER and 9.5% of patients in ODYSSEY OUTCOMES still suffered subsequent ASCVD events. Nevertheless, these trials provide an additional therapeutic option beyond statins and ezetimibe to further reduce ASCVD residual risk. In particular, the FOURIER trial showed a linear trend for lower ASCVD event rates with the lower the LDL-C achieved down to at least 20 mg/dL, with no threshold below which there was any attenuation of benefit achieved[16]. In fact, the prior GLAGOV trial involving the effect of evolocumab on progression of atherosclerosis involving intravascular ultrasound also supported this, showing greater regression of atherosclerosis also down to an LDL-C level of 20 mg/dL with no threshold below which there was any attenuation of benefit[17].

While the PCSK9 monoclonal antibody therapies have the most clinical evidence for reducing ASCVD residual risk, several newer therapies, most of which are still in development, have significant promise for reducing lipid-associated residual risk. Bempedoic acid is an ATP citrate lyase inhibitor which acts in the same pathway as HMG Co-A reductase inhibitor, hence preventing the biosynthesis of cholesterol. It is current FDA approved and indicated in the US for persons with ASCVD or heterozygous familial hypercholesterolemia who may need further LDL-C lowering beyond statin therapy; it may be particular useful for those who are statin intolerant. As monotherapy it reduces LDL-C by approximately 15% and in combination with ezetimibe, approximately 35%. The CLEAR outcomes trial is pending and will demonstrate whether the addition of bempedoic acid beyond statin therapy provides further reduction in ASCVD outcomes[18]. Inclisiran is a small interfering double-stranded RNA which harnesses the natural process of RNAi, is distributed to liver due to GalNAc conjugation, resulting in inhibition of production of PCSK9 specifically, durably and potently. Clinical trials have shown inclisiran to produce a time averaged reduction in LDL-C of approximately 50% after IV injections at baseline, 3 months, and every 6 months later, making this "vaccine" like therapy a potential game changer in lipid management. Whether reducing PCSK9 and therefore LDL-C by this mechanism will result in further reduction in ASCVD outcomes beyond statin therapy is not yet determined, and cardiovascular outcomes trials are underway to examine this in high risk persons with known ASCVD[19]. Inclisiran is current approved in Europe, with approval pending in the United States. Finally, lipoprotein(a) is a significant genetic causal risk factor for ASCVD. Levels of lipoprotein(a) of 70 mg/dL (175 nmol/L) or higher are present in about 15% of the population[20]. Pelacarsen is an antisense oligonucleotide therapy that targets mRNA of lipoprotein(a), reduces lipoprotein(a) levels by up to 80%. A second agent, olpasiran, an si-RNA therapy, lowers lipoprotein(a) levels by up to 90% from early clinical trials[21]. Cardiovascular outcomes trials to examine whether lowering lipoprotein(a) beyond statin therapy with these therapies are in progress.

With recommendations and evidence to support lower LDL-C targets[22] to reduce residual risk, especially among our higher risk patients with ASCVD, the need for additional therapies beyond statins will continue to increase. US guidelines have supported the use of ezetimibe in those with ASCVD where LDL-C still remains at 70 mg/dL despite maximally tolerated statin therapy, and PCSK9i therapy in those at very high risk who still remain above this threshold[3]. European guidelines recommend an LDL-C target of <55 mg/dL for all those with ASCVD (and some primary prevention such as those with diabetes and multiple risk factors), with an option for an LDL-C target of <40 mg/dL with recurrent ASCVD events within 2 years[23]. Most recently, the Lipid Association of India has recommended even lower LDL-C targets of <30 mg/dL in certain extreme risk persons with ASCVD who have other high risk conditions[24].

Therapies for Inflammatory Residual Risk

Increased levels of inflammation, including hs-CRP and IL-6 have been shown to be associated with increased ASCVD risk through numerous studies[25]. Targeting inflammation to reduce ASCVD risk has been of great interest. The JUPITER trial[26] showed rosuvastatin to lower ASCVD events by 44% in persons with "normal" LDL-C who had elevated hs-CRP levels, and those who achieved the lowest levels of both hs-CRP and LDL-C had the lowest rates of ASCVD events[27]. However, since statins lower both LDL-C and hs-CRP, and the independent effect of lowering hs-CRP on ASCVD events was never demonstrated, this trial did not prove the inflammation hypothesis. CANTOS[28] was the first demonstration of proof-of-concept for lowering inflammation to reduce ASCVD events. In this trial, canakinumab, which lowers IL-6 by more than 40% and hs-CRP levels by more than 50%, was shown to reduce subsequent ASCVD events by 15% in those with prior CVD; however, the expense of this therapy as well as increased rate of fatal infections precluded it from receiving an indication nor recommendation in guidelines for lowering inflammation to reduce CVD. In the Cardiovascular Inflammation Reduction Trial (CIRT), administration of low dose methotrexate did not reduce cardiovascular outcomes and the trial was terminated early due to futility[29]. Finally, the COLCOT trial investigated the efficacy of colchicine in reducing cardiovascular outcomes in persons with a prior myocardial infarction. This resulted in a 23% relative risk reduction for the primary cardiovascular endpoint[30]. While both CANTOS and COLCOT show that selective

reduction of inflammation may further lower ASCVD risk, national guidelines have yet to adopt any anti-inflammatory therapy for reduction of ASCVD risk.

Therapies for Metabolic Residual Risk

Since 2008 US FDA guidance has required all new diabetes therapies to show cardiovascular benefit. The advent of the sodium glucose lowering transport-2 inhibitors (SGLT2i) and glucagon like peptide-1 receptor agonists (GLP1-RA) in recent years have brought about a revolution not only in diabetes treatments, but more importantly cardiovascular risk reduction. The EMPA-REG trial[31] involving empagliflozin and CANVAS trial[32] involving canagliflozin were the first of the SGLT2i trials in persons with diabetes to show reductions in CVD outcomes and importantly showed significant reductions in heart failure incidence to be a major drive of the CVD reductions. Dapagliflozin in the DECLARE trial[33] also showed reductions in the composite of heart failure hospitalizations and CVD death (although not the co-primary cardiovascular composite outcome). Importantly, in persons with heart failure with reduced ejection fraction (HFrEF), both empagliflozin and dapagliflozin have been shown to reduce the composite heart failure endpoint[34,35]; empagliflozin also is the first SGLT2i to additionally benefit persons with heart failure with preserved ejection fraction (HFpEF)[36]. Moreover, SGLT2i therapies significantly benefit renal outcomes in persons with established chronic kidney disease[37,38], and thus are rapidly becoming standard of care therapies for such individuals. As for GLP1-RA therapies, liraglutide in the LEADER trial[39] showed cardiovascular event risk reductions in persons with diabetes, which included those with and without prior CVD. Semaglutide also benefitted persons with diabetes with significant reductions observed in the primary cardiovascular endpoints both in the SUSTAIN-6[40] and PIONEER-6[41] trials; in SUSTAIN-6 there was also a dramatic 39% reduction in stroke incidence, a secondary endpoint. Currently, both SGLT2i and GLP1-RA therapies indicated by several guidelines for the reduction of CVD events in persons with diabetes with either pre-existing CVD or multiple risk factors, irrespective of metformin use or initiation or target HbA1c level[42]. The recently released STEP 1 trial[43] involving a higher dosage of semaglutide (2.4 mg weekly) given to overweight and obese adults showed a dramatic a 15% reduction in weight, making this a significant advance in weight loss therapies. Of note, a cardiovascular outcomes trial involving this higher dosage of semaglutide given to persons with known ASCVD who also are overweight or obese is ongoing and will provide valuable data on the efficacy of this therapy in reducing CVD outcomes beyond that shown already among diabetes patients.

The other great advance this decade in metabolic therapies for reducing ASCVD risk is the demonstrated cardiovascular outcomes benefit of icosapent ethyl therapy, shown initially among Japanese patients in the JELIS trial[44] among patients in Japan, but much more broadly in the multinational REDUCE-IT trial (Figure 5)[45]. While specifically indicated for persons with moderate elevations

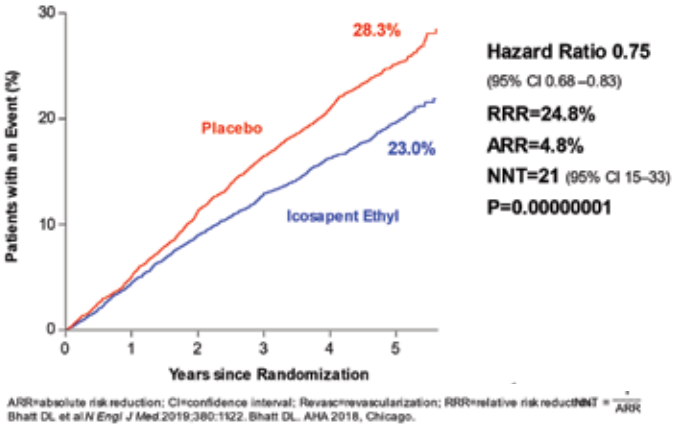


Figure 4. REDDUCE-IT Primary endpoint: Death, MI, stroke, coronary revasc, unstable angina

in triglycerides (who also have either prior ASCVD or diabetes and multiple risk factors), the benefits of icosapent ethyl (pure EPA) appear to be independent of their triglyceride-lowering effect, involving antioxidant, anti-inflammatory and membrane stabilizing effects, hence their consideration here more generally as a metabolic agent. In the REDDUCE-IT trial, beyond statin therapy, icosapent ethyl therapy was shown to be associated with a further 25% relative risk reduction of the primary composite endpoint, with every secondary endpoint in hierarchical analysis met, with the exception of total mortality. The failure of other clinical trials of omega-3 fatty acid therapies, including combination EPA-DHA therapies, such as the recent STRENGTH trial[46] underscores the point that the REDUCE-IT trial implications should not be extended beyond icosapent ethyl. Only prescription icosapent ethyl therapy is indicated for cardiovascular event risk reduction and guidelines specify their use for persons with pre-existing ASCVD or diabetes with multiple risk factors and triglycerides of 135-499 mg/dl beyond statin therapy. Dietary supplement omega 3 fatty acid supplements often have impurities such as saturated and other fats, are oxidized, and none have been shown to reduce cardiovascular events.

Therapies for Thrombotic Residual Risk

Recent recommendations[47] have brought into question the appropriateness of aspirin therapy for primary prevention of cardiovascular disease due to questionable net clinical benefit from bleeding risks that largely counterbalance any cardiovascular benefits However, in patients with known ASCVD, effective antithrombotic therapy is standard of care, but despite aspirin therapy, events still occur, demonstrating significant thrombotic residual risk and thus the need for intensification of thrombotic therapy. Two trials of low dose rivaroxaban therapy have shown cardiovascular benefit. In the ATLAS ACS 2-TIMI 51 trial involving rivaroxaban 2.5mg or 5 mg added to other antiplatelet therapy (93% on dual antiplatelet therapy) a 16% relative risk reduction in major adverse cardiovascular events47 was shown, although this was offset by a 1.5% absolute risk increase in major bleeding. COMPASS, however, showed low-dose rivaroxaban therapy plus aspirin vs aspirin alone to have a

24% reduction in the primary outcome, with a 22% reduction in the net clinical benefit endpoint which was a composite of the primary outcome and fatal or symptomatic bleeding[48].

In addition, while the use of dual antiplatelet therapy (DAPT) for 1 year post-PCI has been a standard of care, its benefits from longer term treatment have only recently been demonstrated. In the PEGASUS TIMI-55 trial the additional of ticagrelor to aspirin in patients with a prior myocardial infarction showed a 16% reduction in MACE[49], and a subsequent meta-analysis of several trials in the post-ACS setting has shown similar benefits, but the benefits appear to be substantially counterbalanced by major bleeding. Further, among patients with diabetes and stable CAD with a history of PCI or bypass surgery, THEMIS-PCI showed from ticagrelor a reduction in the composite MACE endpoint, but also a significantly higher occurrence of major bleeding[50].

Conclusions

Despite currently approved standard of care therapies for persons with ASCVD, substantial residual risk exists, especially in those defined as "very high risk" according to current guidelines. While firmly entrenched into the guidelines for those with ASCVD, these therapies are still significantly underutilized, such as high intensity statins (51) and call for more aggressive efforts to address issues with clinical inertia. The advent of newer lipid, anti-inflammatory, metabolic, and antithrombotic therapies hold promise for further reducing this residual risk; however, costs and/or guideline restrictions to use in only those at highest risk (or not at all in the case of anti-inflammatory therapies) have limited their availability and overall impact on cardiovascular events globally. The hopeful demonstration of newer therapies in development with pending cardiovascular outcomes trials will hopefully add to the clinician's armamentarium of therapies to address ASCVD residual risk. Moreover, a greater emphasis and resources devoted towards lifestyle modification efforts remains central for population-wide cardiovascular risk reduction efforts.

References

1. Wong ND, Zhao Y, Xiang P, et al. Five-year residual atherosclerotic cardiovascular disease risk prediction model for statin treated patients with known cardiovascular disease. Am J Cardiol 2020;137:7-11. doi: 10.1016/j.amjcard.2020.09.043. Epub 2020 Sep 28. PMID: 32991855; PMCID: PMC7704850.
2. Colantonio LD, Shannon ED, Orroth KK, et al. Ischemic event rates in very-high-risk adults. J Am Coll Cardiol 2019;74(20):2496-2507. doi: 10.1016/j.jacc.2019.09.025. PMID: 31727288.
3. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2019;139(25):e1082-e1143. doi: 10.1161/CIR.0000000000000625. Epub 2018 Nov 10. Erratum in: Circulation. 2019 Jun 18;139(25):e1182-e1186. PMID: 30586774; PMCID: PMC7403606.
4. Fonarow GC, Gawlinski A. Rationale and design of the cardiac hospitalization atherosclerosis management program at the University of California Los Angeles. Am J Cardiol 2000;85(3A):10A-17A. doi: 10.1016/s0002-9149(99)00933-9. PMID: 10695702.
5. Yusuf S. Two decades of progress in preventing vascular disease. Lancet 2002;360(9326):2-3. doi: 10.1016/S0140-6736(02)09358-3. PMID: 12114031.
6. Sabatine MS, Giugliano RP, Keech AC, et al; FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med 2017; 376(18):1713-1722. doi: 10.1056/NEJMoa1615664. Epub 2017 Mar 17. PMID: 28304224.
7. Schwartz GG, Steg PG, Szarek M, et al; ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med 2018; 379(22):2097-2107. doi: 10.1056/NEJMoa1801174. Epub 2018 Nov 7. PMID: 30403574.
8. Eckel RH, Jakicic JM, Ard JD, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129(25 Suppl 2):S76-99. doi: 10.1161/01.cir.0000437740.48606.d1. Epub 2013 Nov 12. Erratum in: Circulation. 2014 Jun 24;129(25 Suppl 2):S100-1. Erratum in: Circulation 2015;131(4):e326. PMID: 24222015.
9. Hussain A, Ballantyne CM. New Approaches for the Prevention and Treatment of Cardiovascular Disease: Focus on Lipoproteins and Inflammation. Annu Rev Med 2021;72:431-446. doi: 10.1146/annurev-med-100119-013612. Epub 2020 Nov 20. PMID: 33217249.
10. AIM-HIGH Investigators, Boden WE, Probstfield JL, Anderson T, et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. N Engl J Med 2011;365(24):2255-67. doi: 10.1056/NEJMoa1107579. Epub 2011 Nov 15. Erratum in: N Engl J Med. 2012 Jul 12;367(2):189. PMID: 22085343.
11. HPS2-THRIVE Collaborative Group, Landray MJ, Haynes R, et al. Effects of extended-release niacin with laropiprant in high-risk patients. N Engl J Med 2014;371(3):203-12. doi: 10.1056/NEJMoa1300955. PMID: 25014686.
12. Taheri H, Filion KB, Windle SB, et al. Cholesteryl ester transfer protein inhibitors and cardiovascular outcomes: A systematic review and meta-analysis of randomized controlled trials. Cardiology 2020;145(4):236-250. doi: 10.1159/000505365. Epub 2020 Mar 13. PMID: 32172237.
13. Okopień B, Buldak L, Bołdys A. Fibrates in the management of atherogenic dyslipidemia. Expert Rev Cardiovasc Ther 2017;15(12):913-921. doi: 10.1080/14779072.2017.1408410. Epub 2017 Nov 28. PMID: 29183206.
14. Pradhan AD, Paynter NP, Everett BM, Glynn RJ, Amarenco P, Elam M, Ginsberg H, Hiatt WR, Ishibashi S, Koenig W, Nordestgaard BG, Fruchart JC, Libby P, Ridker PM. Rationale and design of the pemafibrate to reduce cardiovascular outcomes by reducing triglycerides in patients with diabetes (PROMINENT) study. Am Heart J 2018;206:80-93. doi: 10.1016/j.ahj.2018.09.011. Epub 2018 Sep 29. PMID: 30342298.
15. Cannon CP, Blazing MA, Giugliano RP, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372(25):2387-97. doi: 10.1056/NEJMoa1410489. Epub 2015 Jun 3. PMID: 26039521.
16. Giugliano RP, Pedersen TR, Park JG, et al. Clinical efficacy and safety of achieving very low LDL-cholesterol concentrations with the PCSK9 inhibitor evolocumab: a pre-specified secondary analysis of the FOURIER trial. Lancet 2017; 390:1962-1971.
17. Nicholls SJ, Puri R, Anderson T, et al. Effect of evolocumab on progression of coronary disease in statin-treated patients: The GLAGOV randomized clinical trial. JAMA 2016;316(22):2373-2384. doi: 10.1001/jama.2016.16951. PMID: 27846344.
18. Ballantyne CM, Bays H, Catapano AL, Goldberg A, Ray KK, Saseen JJ. Role of bempedoic acid in clinical practice. Cardiovasc Drugs Ther 2021;35(4):853-864. doi: 10.1007/s10557-021-07147-5. Epub 2021 Apr 5. Erratum in: Cardiovasc Drugs Ther. 2021 Apr 19;: PMID: 33818688; PMCID: PMC8266788.
19. Brandts J, Ray KK. Clinical implications and outcomes of the ORION Phase III trials. Future Cardiol 2021;17(5):769-777. doi: 10.2217/fca-2020-0150. Epub 2020 Dec 21. PMID: 33345605.
20. Tsimikas S, Moriarty PM, Stroes ES. Emerging RNA therapeutics to lower blood levels of Lp(a): JACC Focus Seminar 2/4. J Am Coll

Cardiol 2021;77(12):1576-1589. doi: 10.1016/j.jacc.2021.01.051. PMID: 33766265.
21. Miname MH, Rocha VZ, Santos RD. The role of RNA-targeted therapeutics to reduce ASCVD risk: What have we learned recently? Curr Atheroscler Rep 2021;23(8):40. doi: 10.1007/s11883-021-00936-1. PMID: 34146170.
22. Wong ND, Puri R, Mehta V, Duell PB. When is it appropriate to lower low density lipoprotein-cholesterol levels to <30 mg/dL? Am J Cardiol 2021;157:142-144. doi: 10.1016/j.amjcard.2021.06.041. Epub 2021 Aug 1. PMID: 34344510.
23. Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis 2019;290:140-205. doi: 10.1016/j.atherosclerosis.2019.08.014. Epub 2019 Aug 31. Erratum in: Atherosclerosis. 2020 Jan;292:160-162. Erratum in: Atherosclerosis. 2020 Feb;294:80-82. PMID: 31591002.
24. Puri R, Mehta V, Iyengar SS, et al. Low density lipoprotein cholesterol targets in secondary prevention of atherosclerotic cardiovascular disease. J Assoc Physicians India 2020;68(11[Special]):21-34. PMID: 33350612.
25. Lawler PR, Bhatt DL, Godoy LC, et al. Targeting cardiovascular inflammation: next steps in clinical translation. Eur Heart J 2021;42(1):113-131. doi: 10.1093/eurheartj/ehaa099. PMID: 32176778.
26. Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359(21):2195-207. doi: 10.1056/NEJMoa0807646. Epub 2008 Nov 9. PMID: 18997196.
27. Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Trial Study Group. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet 2009;373(9670):1175-82. doi: 10.1016/S0140-6736(09)60447-5. Epub 2009 Mar 28. PMID: 19329177.
28. Ridker PM, Everett BM, Thuren T, et al; CANTOS Trial Group. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N Engl J Med 2017;377(12):1119-1131. doi: 10.1056/NEJMoa1707914. Epub 2017 Aug 27. PMID: 28845751.
29. Ridker PM, Everett BM, Pradhan A, et al; CIRT Investigators. Low-dose methotrexate for the prevention of atherosclerotic events. N Engl J Med 2019;380(8):752-762. doi: 10.1056/NEJMoa1809798. Epub 2018 Nov 10. PMID: 30415610; PMCID: PMC6587584.
30. Tardif JC, Kouz S, Waters DD, et al. Efficacy and safety of low-dose colchicine after myocardial infarction. N Engl J Med 2019;381(26):2497-2505. doi: 10.1056/NEJMoa1912388. Epub 2019 Nov 16. PMID: 31733140.
31. Zinman B, Wanner C, Lachin JM, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373(22):2117-28. doi: 10.1056/NEJMoa1504720. Epub 2015 Sep 17. PMID: 26378978.
32. Neal B, Perkovic V, Mahaffey KW, et al; CANVAS Program Collaborative Group. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377(7):644-657. doi: 10.1056/NEJMoa1611925. Epub 2017 Jun 12. PMID: 28605608.
33. Wiviott SD, Raz I, Bonaca MP, et al; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380(4):347-357. doi: 10.1056/NEJMoa1812389. Epub 2018 Nov 10. PMID: 30415602.
34. McMurray JJV, Solomon SD, Inzucchi SE, et al; DAPA-HF Trial Committees and Investigators. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381(21):1995-2008. doi: 10.1056/NEJMoa1911303. Epub 2019 Sep 19. PMID: 31535829.
35. Packer M, Anker SD, Butler J, et al; EMPEROR-Reduced Trial Investigators. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med 2020;383(15):1413-1424. doi: 10.1056/NEJMoa2022190. Epub 2020 Aug 28. PMID: 32865377.
36. Anker SD, Butler J, Filippatos G, et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med 2021;385(16):1451-1461. doi: 10.1056/NEJMoa2107038. Epub 2021 Aug 27. PMID: 34449189.
37. Perkovic V, Jardine MJ, Neal B, et al; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380(24):2295-2306. doi: 10.1056/NEJMoa1811744. Epub 2019 Apr 14. PMID: 30990260.
38. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383(15):1436-1446. doi: 10.1056/NEJMoa2024816. Epub 2020 Sep 24. PMID: 32970396.
39. Marso SP, Daniels GH, Brown-Frandsen K, et al; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375(4):311-22. doi: 10.1056/NEJMoa1603827. Epub 2016 Jun 13. PMID: 27295427; PMCID: PMC4985288.
40. Marso SP, Bain SC, Consoli A, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375(19):1834-1844. doi: 10.1056/NEJMoa1607141. Epub 2016 Sep 15. PMID: 27633186.
41. Husain M, Birkenfeld AL, Donsmark M, et al; PIONEER 6 Investigators. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2019;381(9):841-851. doi: 10.1056/NEJMoa1901118. Epub 2019 Jun 11. PMID: 31185157.
42. Wilding JPH, Batterham RL, Calanna S, et al STEP 1 Study Group. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384(11):989. doi: 10.1056/NEJMoa2032183. Epub 2021 Feb 10. PMID: 33567185.
43. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: *Standards of Medical Care in Diabetes-2021*. Diabetes Care. 2021 Jan;44(Suppl 1):S111-S124. doi: 10.2337/dc21-S009. PMID: 33298420.
44. Yokoyama M, Origasa H, Matsuzaki M, et al; Japan EPA lipid intervention study (JELIS) Investigators. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 2007;369(9567):1090-8. doi: 10.1016/S0140-6736(07)60527-3. Erratum in: Lancet. 2007 Jul 21;370(9583):220. PMID: 17398308.
45. Bhatt DL, Steg PG, Miller M, et al; REDUCE-IT Investigators. Cardiovascular risk reduction with icosapent ethyl for hypertriglyceridemia. N Engl J Med 2019;380(1):11-22. doi: 10.1056/NEJMoa1812792. Epub 2018 Nov 10. PMID: 30415628.
46. Nicholls SJ, Lincoff AM, Garcia M, et al. Effect of high-dose omega-3 fatty acids vs corn oil on major adverse cardiovascular events in patients at high cardiovascular risk: The STRENGTH Randomized Clinical Trial. JAMA 2020;324(22):2268-2280. doi: 10.1001/jama.2020.22258. PMID: 33190147; PMCID: PMC7667577.
47. Mega JL, Braunwald E, Wiviott SD, et al; ATLAS ACS 2–TIMI 51 Investigators. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med 2012;366(1):9-19. doi: 10.1056/NEJMoa1112277. Epub 2011 Nov 13. PMID: 22077192.
48. Eikelboom JW, Connolly SJ, Bosch J, et al; COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017;377(14):1319-1330. doi: 10.1056/NEJMoa1709118. Epub 2017 Aug 27. PMID: 28844192.
49. Bonaca MP, Bhatt DL, Cohen M, et al; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372(19):1791-800. doi: 10.1056/NEJMoa1500857. Epub 2015 Mar 14. PMID: 25773268.
50. Bhatt DL, Steg PG, Mehta SR, et al; THEMIS Steering Committee and Investigators. Ticagrelor in patients with diabetes and stable coronary artery disease with a history of previous percutaneous coronary intervention (THEMIS-PCI): a phase 3, placebo-controlled, randomised trial. Lancet 2019;394(10204):1169-1180. doi: 10.1016/S0140-6736(19)31887-2. Epub 2019 Sep 1. PMID: 31484629.
51. Klimchak AC, Patel MY, Iorga ŞR, Kulkarni N, Wong ND. Lipid treatment and goal attainment characteristics among persons with atherosclerotic cardiovascular disease in the United States. Am J Prev Cardiol 2020;1:100010. doi: 10.1016/j.ajpc.2020.100010. Erratum in: Am J Prev Cardiol. 2021 Mar 29;5:100160. PMID: 34327452; PMCID: PMC8315384.

Srce i krvni sudovi 2021; 40(4): 257-260

Review article

Chronic total occlusions: What's new?

Aleksandr Osiev[1], Vladimir Mitov[2], Egor Malakhov[1]
[1]JSC MEDSI, Moscow, Russian Federation, [2]Medical center Zajecar, Serbia

Cardiovascular interventions is a fast-evolving specialty. New technologies and devices become available every year. Interventionists should be aware about current and future developments to be at best in providing patient care. Chronic total occlusion (CTO) is a challenging situation for a specialist, even for an experienced one, as the lesions require a special approach. The article contains the latest information regarding CTO treatment strategies and outcomes.

Chronic total occlusions are identified in 15–30% of all patients referred for coronary angiography and considered as 100% coronary lesion of more than 3 months evolution[1]. It is argued there are collaterals in the CTO situation, and optimal medical therapy is a good option. Unfortunately, collaterals provide 40% of antegrade blood flow at rest, and only 10% during stress[2]. Recent study of MA et al. using single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) revealed CTO-related ischemia is an independent predictor for adverse events[3]. Systematic review and a meta-analysis of contemporary studies including 6,084 patients with a median of 12-months follow up showed that successful CTO PCI was associated with a lower incidence of MACE driven by lower all-cause mortality compared with failed CTO PCI at a median follow-up of 1 year[4]. According to a meta-analysis of 34 studies, CTO recanalization results in improvement of LVEF, reduction of adverse remodeling and an improvement of survival[5]. Study of Rha et al. demonstrated that successful CTO PCI with DESs was associated with a higher risk of repeat PCI for the target vessel, but showed a reduced incidence of death or MI[6]. Ten-year results of CTO recanalization provided by Park et at. showed late survival benefit after CTO PCI as a primary treatment strategy compared to optimal medical therapy. There was no difference during the first three years, but at the time interval between 3 and 10 years, relative reduction of cardiac deaths became apparent (Figure 1)[7].

There are no randomized trials regarding late CTO recanalization results, but available data clearly tells us PCI improves survival.

Three main algorithms for CTO procedures are presented in literature: EuroCTO (Figure 2, modified hybrid algorithm[8], Asia Pacific (Figure 3)[9] and North American (Figure 4)[10]. All approaches contain similar angiographic criteria regarding antegrade or retrograde initial recanalization strategy, Stingray System (Boston Scientific) use. Asia Pacific and EuroCTO algorithms contain more details, such as IVUS for proximal cap puncture, CrossBoss (Boston Scientific, Natick, Massachusetts) catheter use for in-stent CTO, criteria for knuckle-wiring and information on when to stop the procedure. The algorithms represent a useful toolset and guidance for all CTO operators.

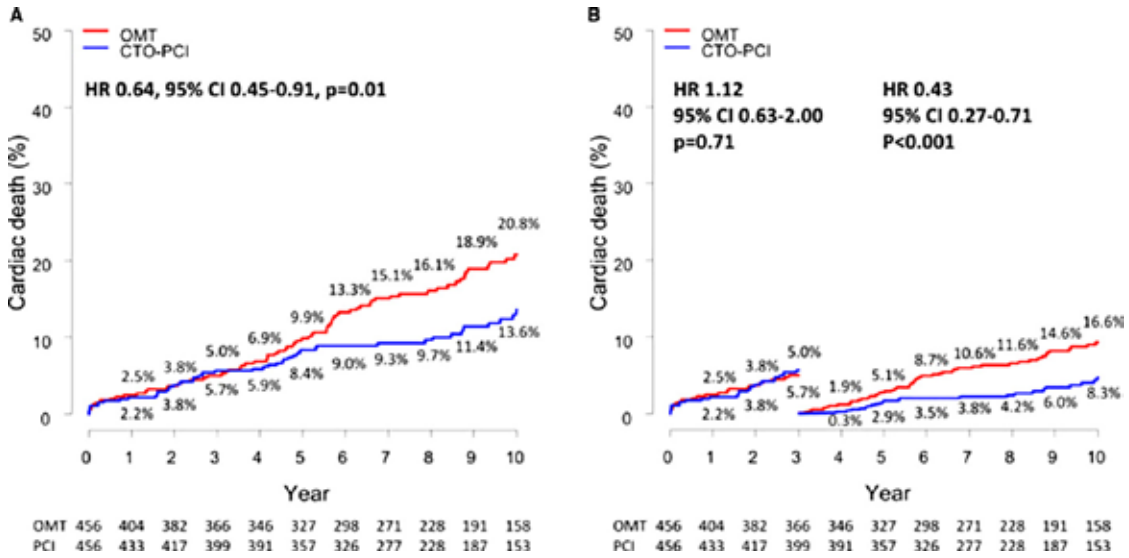


Figure 1. Kaplan-Meier event curves at 10 years and 3-year landmark analysis for cardiac death. **A,** 10-year cumulative event curves for cardiac death. **B,** Time-to-event curves with landmark analysis from 0 to 3 and 3 to 10 years for cardiac death. CTO indicates chronic total occlusion; HR, hazard ratio; OMT, optimal medical therapy; and PCI, percutaneous coronary intervention.

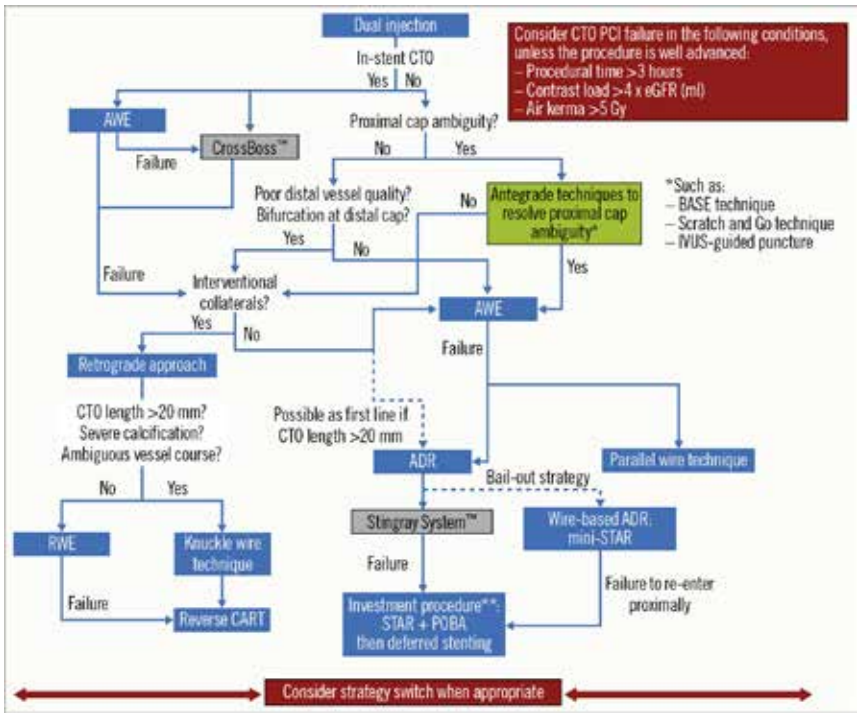


Figure 2. Modified hybrid algorithm for CTO PCI
ADR: antegrade dissection re-entry; AWE: antegrade wire escalation; BASE: balloon-assisted subintimal entry; CART: controlled antegrade retrograde tracking; CTO: chronic total occlusion; eGFR: estimated glomerular filtration rate; IVUS: intravascular ultrasound; PCI: percutaneous coronary intervention; POBA: plain old balloon angioplasty; RWE: retrograde wire escalation; STAR: subintimal tracking and re-entry.

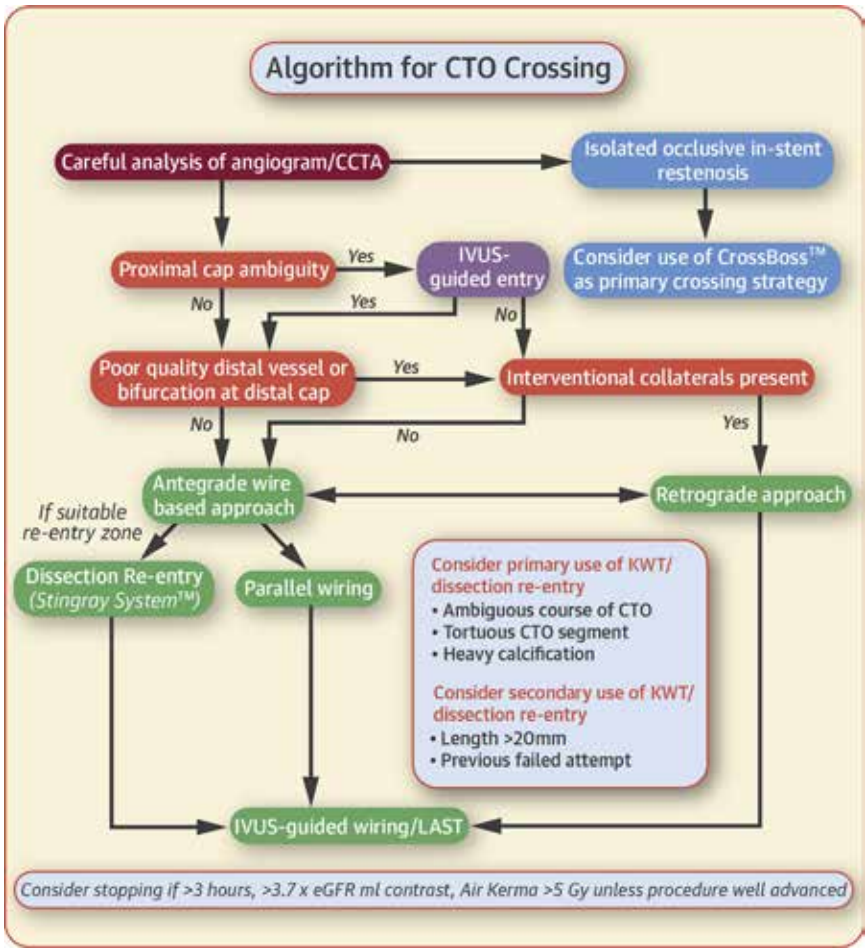


Figure 3. Asia-Pacific CTO club algorithm
eGFR - estimated glomerularfiltration rate; IVUS - intravascular ultrasound; KWT - knuckle wire technique; LAST - limited antegrade subintimaltracking;

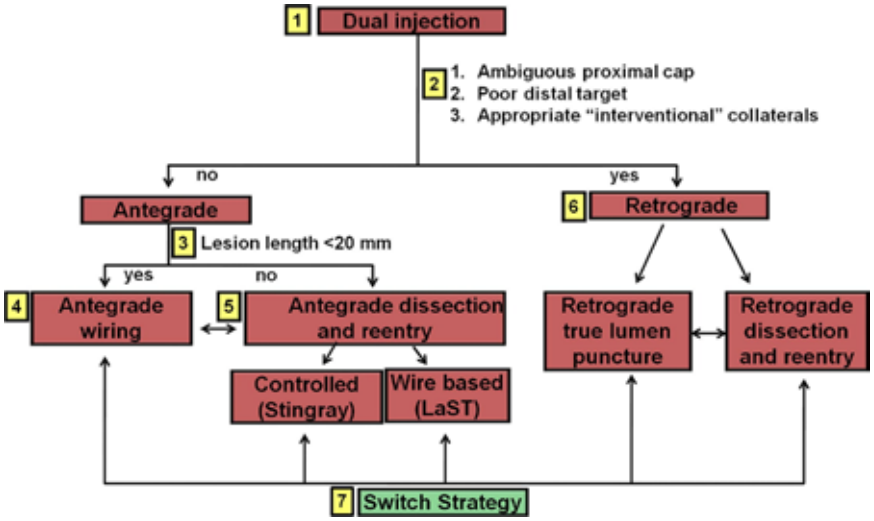


Figure 4. North American CTO algorithm
The algorithm starts with dual coronary injection (box 1) to allow assessment of several angiographic parameters (box 2) and allow selection of a primary antegrade (boxes 3 to 5) or primary retrograde (box 6) strategy. Strategy changes are made (box 7), depending on the progress of the case. CTO = chronic total occlusion; LaST = limited antegrade subintimal tracking.

Certainly, operator experience plays a key role in CTO interventions, but success also depends on tools and devices:

- Stingray LP (Boston Scientific), CTO re-entry system that helps to enter true lumen.
- CrossBoss (Boston Scientific), coronary CTO crossing catheter for subintimal space and true lumen;
- SUOH03 (ASAHI Intecc), an ultra-ow tipload guidewire (0.3 gf) for collateral tortuosities;
- Gaia Next (ASAHI Intecc), preshaped, cone-tipped CTO-dedicated guidewires family (Gaia Next 1, 2 gf tipload; Gaia Next 2, 4 gf tipload; Gaia Next 3, 6gf tipload);
- Judo Sentai (Boston Scientific), 0.008" tapered guidewires family (Judo 1, soft intraluminal crossing wire for antegrade microchannels, 1 gf tipload; Judo 3, intraluminal crossing wire for fibro-calcific lesions, 3 gf tipload; Judo 6, penetration wire with excellent steerability in tight lesions, 6 gf tipload).

Atherectomy is also a useful option, according to analysis of the PROGRESS-CTO registry: currently it is performed in approximately 3% of CTO PCI cases and associated with similar technical and procedural success and overall major cardiac events rates, but higher risk of donor vessel injury and tamponade[11]. When it comes to techniques, both subintimal and intraplaque recanalization approaches to CTO are associated with comparable mid-term angiographic results[12]. Modified STRAW is a novel technique presented by Vo, Minh N., et al. describes microcatheter use to decompress proximal hematoma and facilitate wire re-entry with a stingray (Boston Scientific)[13]. Antegrade fenestration and reentry (AFR) technique described by Carlino, Mauro, et al. causes extraplaque disruption of the vessel with 1:1-sized balloon catheter in the CTO body. The technique creates tears of the media, and aids soft wire to reach true lumen distally[14]. Using drug-coated balloon catheters after subintimal plaque modification in failed coronary CTO intervention and delayed (30 days to several months) repeat attempt with deferred stenting is another novel technique in complex cases[15]. Moreover, moderate-severe calcification is frequently found in CTOs. Intravascular lithotripsy could also improve outcomes along with atherectomy techniques[16]. Another valuable option for calcified lesions preparation and recoil decrease is super-high pressure balloon dilatation (SIS Medical)[17].

In conclusion, a CTO is a complex situation for an interventionist. Occluded arteries cause impact on quality of life and survival. Current technologies and operator experience significantly increased procedure success rate. We have a great toolbox nowadays, but needless to say, novel techniques and devices are required to improve outcomes, i.e., dedicated guidewires, microcatheters. There is always room for improvement. It would be nice to have new CTO guidelines consolidating available data that will help operators to take right decisions, making CTO procedures safer and widely used.

References

1. Montalescot G, Sechtem U, Achenbach S, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. Eur Heart J 2013;34:2949–3003.
2. Werner GS, et al. "The functional reserve of collaterals supplying long-term chronic total coronary occlusions in patients without prior myocardial infarction." Eur Heart J 2006;20: 2406-2412.
3. Xinghong M, et al. Predictive value of SPECT myocardial perfusion imaging in patients with unrevascularized coronary chronic total occlusion. Ann Nucl Med 2021: 1-9.
4. Megaly M, et al. Outcomes of successful vs. failed contemporary chronic total occlusion percutaneous coronary intervention. Card Interv Ther 2021:1-7.
5. Hoebers LP, et al. Meta-analysis on the impact of percutaneous coronary intervention of chronic total occlusions on left ventricular function and clinical outcome. Int J Cardiol 2015;187:90-96.
6. Rha SW, et al. Five-year outcomes of successful percutaneous coronary intervention with drug-eluting stents versus medical therapy for chronic total occlusions. Yonsei Med J 2018;59:602-610.
7. Park TK, et al. Late survival benefit of percutaneous coronary intervention compared with medical therapy in patients with

coronary chronic total occlusion: a 10-year follow-up study. JAHA 2021;10:e019022.
8. Galassi AR, et al. Percutaneous recanalization of chronic total occlusions: 2019 Consensus. Hospital 2014;84:637-643.
9. Harding SA., et al. A new algorithm for crossing chronic total occlusions from the Asia Pacific Chronic Total Occlusion Club. JACC: Cardiovascular Interventions 2017;21: 2135-2143.
10. Brilakis ES, et al. A percutaneous treatment algorithm for crossing coronary chronic total occlusions. JACC: Cardiovascular Interventions 2012;5:367-379.
11. Xenogiannis I, et al. Usefulness of atherectomy in chronic total occlusion interventions (from the PROGRESS-CTO Registry). Am J Cardiol 2019;123:1422-1428.
12. Xhepa E, et al. Subintimal versus intraplaque recanalization of coronary chronic total occlusions: mid-term angiographic and OCT findings from the ISAR-OCT-CTO registry. JACC: Cardiovascular Interventions 2019;12:1889-1898.
13. Vo MN, et al. Modified subintimal transcatheter withdrawal: A novel technique for hematoma decompression to facilitate distal reentry during coronary chronic total occlusion recanalization." Cath Cardiovasc Interv 2020;96:E98-E101.
14. Carlino M, et al. Antegrade fenestration and re-entry: A new controlled subintimal technique for chronic total occlusion recanalization. Cath Cardiovasc Interv 2018;92:497-504.
15. Ybarra LF, et al. Drug-coated balloon after subintimal plaque modification in failed coronary chronic total occlusion percutaneous coronary intervention: A novel concept. Cath Cardiovasc Interv 2020;96:609-613.
16. Azzalini L, et al. Intravascular lithotripsy in chronic total occlusion percutaneous coronary intervention. EuroIntervention 2019;15:e1025-e1026.
17. Rheude T, et al. Super high-pressure balloon versus scoring balloon to prepare severely calcified coronary lesions: The ISAR-CALC randomized trial." EuroIntervention 2020.

Srce i krvni sudovi 2021; 40(4): 261-263

Review article

Non-invasive testing in chronic coronary syndrome - comparison between functional and anatomic approach

Vojislav Giga[1,2], Nikola Bošković[1], Ana Đorđević-Dikić[1,2] , Ivana Nedeljković[1, 2], Branko Beleslin[1,2]

[1] Cardiology Clinic, University Clinical Center of Serbia, [2] Faculty of Medicine, University of Belgrade

Abstract For the decades, functional testing has been a cornerstone of non-invasive diagnosis and risk stratification in patients with chronic coronary syndromed. With technological improvements coronary CT angiography (CTA) became alterntative method for the assessment of coronary circulation. The aim of this review paper is to show the advantages and limitations of both tecniques and to demonstrate their complementary nature.CTA and functional tests represent complementary methods for the evaluation of patients with chest pain, whereas each method has its place in the diagnostic algorithm. Functional tests are indicated in patients with high clinical probability for the presence of obstructive coronary artery disease for the confirmation of the disease and risk stratification. CTA is indicated in patients with lower clinical probability for the presence of obstructive coronary artery disease when the exclusion of the disease is the major intention. Also, it can be used in patients with chest pain and previous negative functional test in order to establish the presence of non-obstructive vulnerable plaques in order to initiate cardioprotective therapy and prevent future events.

Key words CT coronary angiography, functional testing

For the decades, functional testing has been a cornerstone of non-invasive diagnosis and risk stratification in patients with chronic coronary syndromed. With technological improvements coronary CT angiography (CTA) became alterntative method for the assessment of coronary circulation. The aim of this review paper is to show the advantages and limitations of both tecniques and to demonstrate their complementary nature.

Two recent, randomized studies, PROMISE1 and SCOT-HEART[2], compared prognostic value of functional and anatomical non-invasive testing in patients with chest pain, with pre-test probability for the presence of coronary artery disease of 53%. Patients were randomized on functional testing (68% perfusion scintigraphy, 22% stress echocardiography and 10% stress electrocardiography) or CTA. Half of the patients were women, whereas ¾ of patients had atypical chest pain. The prevalence of obstructive disease on CTA was 11.9% and positive finding on functional test was present in 12.6% of patients. Such a low prevalence of positive functional test is typical in contemporary patients, and can partially be explained by the higher number of patients with atypical symptoms reffered to functional testing as well as with the fact that even in patients with typical symptoms the prevalence of obstructive coronary artery disease is rather low[3]. During the median follow-up of 25 months, there was no significant difference in primary outcome (all-cause mortality, myocardial infarction, unstable angina requiring hospitalization and complications of cardiovascular procedures) between functional (3.0%) and CTA arm (3.3%) of the study.

Data from PROMISE trial clearly demonstrated that the abnormal findings (presence of obstructive stenosis) on non-invasive testing carries poor prognosis, with 3.5 times higher risk of adverse events in comparison to patients with normal findings[4].

On the other hand, patients with completely normal finding on CTA (0% of stenosis) or on functional testing have excellent prognosis. Prevalence of adverse events after negative CTA was 0.93%, confirming further superb negative predictive value of almost 99%[4,5,6]. After negative functional test prevalence of adverse cardiac events was higher (2.09%) in comparison to negative CTA. However, it has been demonstrated that the incidence of obstructive coronary artery disease is increasing in patients with multiple risk factors (Framingham risk score above 20%) even after negative functional test. At contrary incidence of obstructive coronary artery decreases in patients with Framingham risk score below 10% even after positive functional test. If the normal finding on functional test in PROMISE population is defined as the absence of inducible ischemia only in patients with Framingham risk score < 10%, rate of adverse event is almost identical to that of negative CTA (0.92% vs. 0.93%) and corresponds to previously published data[7].

There are several explanations for adverse events after negative functional test, including false negative reading due to low workload and heart rate during test, presence of single vessel disease (especially circumflex artery), drug therapy that modify heart rate and ischemia, and finally presence of balanced ischemia in multi-ves-

Address for correspondence: Vojislav Giga, MD, PhD, Cardiology Clinic, University Clinical center of Serbia; Faculty of Medicine, University of Belgrade.
E-mail: voja2011@yahoo.com

sel disease that is highly relevant mechanism in patients undergoing perfusion scintigraphy. Also, the occurrence of late events can be explained by the progression of the disease itself. In PROMISE trial in patients randomized to functional testing the majority of events occurred in the group of the patients with severe inducible ischemia (large extent of ischemia in LAD territory, or in the territory of other artery with concomitant decrease in EF below 35%, or the presence of ischemia in ≥ 2 territories). The larger the extent of ischemia is, the higher is the risk of adverse events. These findings from PROMISE trial once again confirms the excellent ability of functional test to identify severe coronary artery disease, so this approach is recommended in patients with high clinical probability for the presence of obstructive coronary artery disease.

The major limitation of functional tests is their limited ability to predict the occurrence of acute thrombotic coronary artery occlusion, especially in the presence of mild coronary atherosclerosis. In PROMISE trial absolute number of adverse events was the highest in patients with negative functional test[4], and the explanation is that these events are due to the rupture of nonsignificant plaques that are unable to cause myocardial ischemia detectable with functional test. According to the results of PROMISE trial in patients randomized to CTA the majority of events was in patients with non-obstructive coronary atherosclerosis (stenosis 1-69% in main or side branch or left main stenosis < 50%). The occurrence of acute thrombosis is due to the rupture of vulnerable plaques with thin fibrous cap and large lipid core. The major advantage of CTA is the ability to detect those vulnerable plaques with low attenuation. The risk for plaque rupture and consequent acute coronary event increases with the increase in vulnerable plaques burden. Data form SCOT-HEART study clearly showed that the presence of more than 4% of vulnerable plaques on CTA is related to five times higher risk of fatal or non-fatal myocardial infarction[8]. Similarly is observed in PROMISE trial. The presence of high risk plaques increases risk of adverse cardiovascular events for 70%, irrespective of the presence of other risk factors and the presence of obstructive coronary artery disease. The identification of such plaques is especially important in younger patients and in women with low atherosclerotic burden[9]. That is the reason why CTA is method of choice in patients with chest pain and lower clinical probability of obstructive disease in which negative finding on functional test is expected, but risk of thrombotic events is present. It has been shown in PROMISE trial that 6.5% of vulnerable plaques are prone to rupture[9]. The ability of CTA to detect non-obstructive vulnerable plaques represent the most important explanation for the superiority of CTA in comparison to functional testing (85% of exercise electrocardiography) in the detection of patients at risk of cardiac death or non-fatal myocardial infarction during the 5 years follow-up period (2.3% vs. 3.9%)[2]. It has to be kept in mind that the rate of revascularization was similar between the groups, so the benefit of CTA based approach is predominantly driven by the higher use of cardioprotective drugs (aspirin and statin) (10). The similar pattern of cardioprotective use that leads to plaque stabilization and the prevention of adverse events is also observed in PROMISE trial (11).

Conclusion

CTA and functional tests represent complementary methods for the evaluation of patients with chest pain, whereas each method has its place in the diagnostic algorithm. Functional tests are indicated in patients with high clinical probability for the presence of obstructive coronary artery disease for the confirmation of the disease and risk stratification. CTA is indicated in patients with lower clinical probability for the presence of obstructive coronary artery disease when the exclusion of the disease is the major intention. Also, it can be used in patients with chest pain and previous negative functional test in order to establish the presence of non-obstructive vulnerable plaques in order to initiate cardioprotective therapy and prevent future events.

It should be kept in mind that further testing is not indicated in patients with non-anginal chest pain and normal ECG. Overall, the prognosis of such patients is good with low incidence of fatal and non-fatal myocardial infarction of 0.5% annually[12].

References

1. Douglas PS, Hoffmann U, Patel MR, et al., on behalf of the PROMISE Investigators. Outcomes of Anatomical Versus Functional Testing for Coronary Artery Disease. N Engl J Med 2015;372:1291-1300.
2. Newby DE, Adamson PD, Berry C, et al. Coronary CT angiography and 5-year risk of myocardial infarction. N Engl J Med 2018; 379:924-933.
3. Cheng VY, Berman DS, Rozanski A, et al. Performance of the traditional age, sex, and angina typicality–based approach for estimating pretest probability of angiographically significant coronary artery disease in patients undergoing coronary computed tomographic angiography. Circulation 2011;124: 2423–2432.
4. Hoffmann U, Ferencik M, Udelson JE, et al. ; PROMISE Investigators. Prognostic value of noninvasive cardiovascular testing in patients with stable chest pain: insights from the PROMISE trial (prospective multicenter imaging study for evaluation of chest pain). Circulation 2017;135(24):2320-2332.
5. Bittencourt MS, Hulten E, Ghoshhajra B, et al. Prognostic value of nonobstructive and obstructive coronary artery disease detected by coronary computed tomography angiography to identify cardiovascular events. Circ Cardiovasc Imaging 2014;7(2): 282-291.
6. Hadamitzky M, Täubert S, Deseive S, et al. Prognostic value of coronary computed tomography angiography during 5 years of follow-up in patients with suspected coronary artery disease. Eur Heart J 2013;34(42):3277-3285.
7. Metz LD, Beattie M, Hom R, et al. The prognostic value of normal exercise myocardial perfusion imaging and exercise echocardiography: a meta-analysis. J Am Coll Cardiol 2007;49(2):227-237.
8. Williams MC, Kwiecinski J, Doris M, et al. Low-attenuation noncalcified plaque on coronary computed tomography predicts myocardial infarction: results from the multicenter SCOT-HEART Trial (Scottish Computed Tomography of the HEART). Circulation 2020;141(18):1452-1462.
9. Ferenick M, Mayrhofer T, Bittner DO, et al. Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain. A secondary analysis of the PROMISE randomized clinical trial. JAMA Cardiol 2018; 3(2):144–152.
10. Williams MC, Hunter A, Shah ASV, et al. Use of coronary computed tomographic angiography to guide management of patients with coronary disease. J Am Coll Cardiol 2016;67(15):1759–1768.

11. Ladapo JA, Hoffmann U, Lee KL, et al. Changes in medical therapy and lifestyle after anatomical or functional testing for coronary artery disease. J Am Heart Assoc 2016;5(10):e003807.

12. Adamson PD, Hunter A, Williams MC, et al. Diagnostic and prognostic benefits of computed tomography coronary angiography using the 2016 National Institute for Health and Care Excellence guidance within a randomised trial. Heart 2018; 104:207-214.

Sažetak

Neinvazivni testovi u hroničnom koronarnom sindromu - poređenje funkcionalnog i anatomskog pristupa

Vojislav Giga[1,2], Nikola Bošković[1], Ana Đorđević-Dikić[1,2] , Ivana Nedeljković[1, 2], Branko Beleslin[1,2]

[1]Klinika za kardiologiju, Univerzitetski klinički centar Srbije, [2]Medicinski fakultet, Univerzitet u Beogradu

Dugo vremena neinvazivni funkcionalni testovi su imali vodeću ulogu u dijagnostici i stratifikaciji rizika kod bolesnika sa hroničnim koronarnim sindromom. Međutim, sa tehničkim usavršavanjem, CT koronarna angiografija zauzima važno mesto u neinvazivnoj proceni bolesnika sa bolom u grudima. CT koronarna angiografija i funkcionalni testovi su komplementarne metode u evaluaciji bolesnika sa bolom u grudima, pri čemu svaka ima svoje mesto u dijagnostičkom algoritmu. Funkcionalni testovi su indikovani kod bolesnika sa visokom kliničkom verovatnoćom za postojanje obstruktivne koronarne bolesti, gde testovi potvrđuju dijagnozu i omogućavaju stratifikuju rizika. CT koronarna angiografija je indikovana kod bolesnika sa nižom kliničkom verovatnoćom za postojanje obstruktivne koronarne bolesti kod kojih želimo prvenstveno isključiti prisustvo kornonarne bolesti , a može se razmotriti kod osoba i nakon negativnih funkcionalnih za identifikaciju rasprostranjenosti i karakteristika neobstruktivnih aterosklerotskih plakova i pravovremeno započinjanje kardioprotektivne terapije.

Ključne reči: *CT koronarna angiografija, funkcionalni testovi*

Srce i krvni sudovi 2021; 40(4): 264-267

Special article - Innovations

Telemedicine development in Serbian interventional cardiology

Aleksandar Jolić[1], Milan Nikolić[1], Vladimir Mitov[1], Dragana Adamović[1] ,Marko Dimitrijević[1], Milan Nedeljković[2]

[1]Department of invasive cardiology, Health center Zaječar, [2]Clinic for cardiovascular diseases, University clinical center of Serbia; Medical faculty, University of Belgrade

Abstract Telemedicine includes the use of modern technology, especially two-way interactive audio video communication, computers and telemetry to provide health services to remote patients or to facilitate data exchange between primary care physicians and physically distant specialists. The rough division of systems used for telemedicine purposes (not entering e-health systems as a broader term) is done into systems of the so-called dedicated character, "proprietary" systems, as well as non-dedicated systems.

The first ZASINK was realized in November of 2015, using the dedicated Polycom system (HDX 7000), we realized that the system is able to manage through a very simple and slightly demanding Internet technology (so-called SIP protocol, with a very small request in terms of Internet flow of only 4/4 Mbit / s) this time in the local network, what was enough for us at that moment. By installing a remote controlled camera system (Eagle Eye camera), with the ability to control from a simple remote control and the ability to enter multiple preset camera positions, we eliminated the need for complex, bulky TV equipment, as well as the need for paramedic staff in the cath lab. A video of percutaneous procedures was transmitted in real time from the cath lab from a physical distance of about 500 meters. At the reception end, another Polycom videoconferencing system was used. ZASINK 2017 was held in the "Jezero" hotel on Bor Lake, and then this equipment was successfully used for the first time for transmission outside the local network. The same equipment was used to realize BASICS and "Meet the future od Serbian cardiology" in 2018 and SYNERGY in 2019.

Further improvement of the real-time transmission system has experienced a different format due to COVID19 pandemic outbreak and the need for transmission to be realized in an online format. We developed our non-dedicated system by independently purchasing video, audio, computer equipment and used it for the first time in the realization of ZASINK 2020 in a completely online format with multiple participants from different countries at the same time streaming on the Zoom platform.

By presenting the experience and development of the telemedicine system for the needs of ZASINK Congress, we have shown the possibilities of upgrading and adaptability of the telemedicine system in accordance with the needs and requirements.

Key words telemedicine, videoconferencing; Polycom, dedicated, non-dedicated, ZASINK

Introduction

Historically, the provision of health services necessarily involved physical presence, either the service provider traveled to visit the patient or, more often, the patient traveled to contact the health care provider, which also referred to professional communication between doctors / educators. Travel requires costs, either direct or indirect, delayed treatment, reduced productivity and is time consuming. In fact, travel has significantly participated in the overall cost of the health care system[1]. This has imposed the need to develop a system that would overcome the physical distance between health subjects in order to reduce costs and increase efficiency, especially in countries with a large territory and a scattered population, so that the physically health system is difficult to access. It should start with the broadest terms,

- **e-Health**, as defined by the World Health Organization (WHO) in 2005, is: "an efficient and secure way to use information technologies in support of health and other related fields, including health surveillance, services, literature, and education, knowledge and research."[2]
- **Telemedicine** is a part of e-medicine and e-health and according to the WHO definition: "Providing health services in a way that the patient and the service provider are physically separated, and using information technology to exchange information related to diagnosis and treatment of diseases, injuries, research and

Address for correspondence: Aleksandar Jolić, Department of invasive cardiology, Health center Zaječar, E-mail: jolical149@gmail.com

development, as well as continuous education of medical professionals "[3]

It includes the use of modern technology, especially two-way interactive audio / video communication, computers and telemetry to provide health services to remote patients or to facilitate data exchange between primary care physicians and physically distant specialists[4].

- **TeleHealth** is a broader term than telemedicine, which includes only the use of information technology in remote clinical work. TeleHealth, on the other hand, includes the non-clinical aspect of the remote health care system functioning, such as training and continuous medical education of health professionals, administrative meetings, public health and research purposes[5].

This includes health information systems that serve to collect, process, analyze and receive data needed for the organization and implementation of health care, but also for research and organization in health care [6]. The relationship between telemedicine, teleHealth and eHealth is presented in Figure 1.

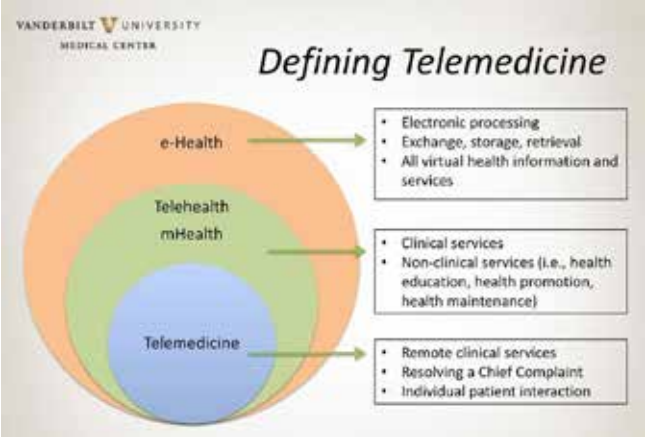


Figure 1. T Relationship between eMedicine, telemedicine and TeleHeath

In accordance with the widespread use of mobile devices in everyday life, another type of application of information technologies for medical purposes is defined by the so-called mobile health (mobileHealth, mHealth). **mHealth** is the use of mobile devices for the purpose of health services, exchange and collection of clinical data[7]. Since 2015, over 165,000 mobile applications related to health and health behavior have been available in online stores[8].

On the other hand, the percentage of households owning a computer in Serbia rose from 50.4% in 2010 to 74.3% in 2020, in the same year 80% of households owned broadband internet and 94.1% owned a mobile phone[9].

E-learning is used in 84% of countries around the world, 47% of WHO members use some form of electronic records, 80% of countries report the use of social networks in health promotion[3].

The rough division of systems used for telemedicine purposes (not entering e-health systems as a broader term) is done into systems of the so-called **dedicated** character, "proprietary" systems, as well as **non-dedicated** systems. Perhaps the difference between these two groups of systems should be described as "plug over play" in the former, and "plug and stay to play" in the latter. By installing a remote controlled camera system (Eagle Eye camera), with the ability to control from a simple remote control and the ability to enter multiple preset camera positions, we eliminated the need for complex, bulky TV equipment, as well as the need for paramedic staff in the cath lab. At the reception end, another Polycom videoconferencing system was used.

ZASINK telemedicine development

In March 2014, the Department of Invasive Cardiology of the Health Center Zajecar was opened as a section for providing coronary angiography, elective and primary percutaneous coronary angioplasty services for the area of eastern Serbia with a gravitational population of about 245,000. As the clinical experience accumulated, there was a need to connect with experts in the field of invasive cardiology from tertiary health care institutions, as well as with local cardiologists and health centers, all in order to improve clinical work and exchange experiences in the treatment of complex cardiac patients.

Everything was based on experiences in the application of IT technologies, using the electronic records system of the Ministry of Health of the Republic of Serbia - "ZIS-Health Information System", which has been in active use since 2012 in our health center. Dedicated equipment used nowadays ZC Zajecar received in 2011 as part of a telemedicine project implemented under the auspices of NALED, the Ministry of Health, and a donation from the "Merck" company, when the equipment from the "Polycom" company was obtained. KC Nis received the same set of equipment, as well as DZ Boljevac, for the purpose of achieving professional communication related to diagnostics and therapy.

On this basis, the first ZAjecar Symposium of Interventional Cardiology (ZASINK) was realized in November 2015 with the participation of eminent lecturers in the field of interventional cardiology from university clinical centers. In the preparation of this event, there was a need for direct transfer of intervention procedures from the cath lab to the venue of the event, which was then the amphitheater of the Health center of Zajecar. Simultaneously with live transmission the lectures were held. Initially, the idea was based on the use of TV systems, which in turn required the presence of complete equipment for the so-called "live" image transmission, as well as the presence of bulky equipment in the cath lab and staff who are not educated to work in sterile medical procedure environment. Insight into the features of the Polycom system (HDX 7000), we realized that the system is able to manage through a very simple and slightly demanding Internet technology (so-called SIP protocol, with a very small request in terms of Internet flow of only 4/4 Mbit / s) this time in the local network, what was enough for us at that moment. By installing a remote controlled camera system (Eagle Eye camera), with the ability to control from a simple remote control and the ability to enter multiple preset camera posi-

Figure 2. The first real time cath lab transmission using local network

Figure 3. The first real time cath lab transmission outside the local network (using internet)

tions, we eliminated the need for complex, bulky TV equipment, as well as the need for paramedic staff in the cath lab (Figure 2).

On the other hand, courtesy of the Siemens Serbia service technicians, we got a so-called "parasitic" output from the screen (note, which is a very simple technology that every desktop PC has), i.e. the so-called "imager", which simply connected to the PC input of the Polycom system, was visible at the reception end. Until then, the broadcasts from the cath lab took place by recording the screen of the imager in the cath lab with a professional TV camera! These first steps were characterized by the transmission of sound through a conference, i.e. "desktop" microphone, which provided satisfactory sound quality for the time.

A video of percutaneous procedures was transmitted in real time from the cath lab from a physical distance of about 500 meters. At the reception end, another Polycom videoconferencing system was used (courtesy of the staff of the health center in Boljevac).

The application of this system was used again in 2016, also for the transfer to the amphitheater of DZ Zajecar. ZASINK 2017 was held in the "Jezero" hotel on Bor Lake, and then this equipment was successfully used for the first time for transmission outside the local network (Figure 3).

The use of this equipment did not go unnoticed by the cardiology community in Serbia, and the same equipment is used for transmission from 3 different points, cath labs in KC of Serbia, IKVB Vojvodina to the main room at BASICS in 2018, as a leading professional meeting from the field of interventional cardiology in Serbia. In the same year, both systems from eastern Serbia (Zajecar and Boljevac) were used in the realization of the meeting "Meet the future of Serbian cardiology" organized by the Institute for Cardiovascular Diseases, Sremska Kamenca. The equipment was used to assist in the realization of the "SYNERGY" meeting in 2019.

Further improvement of the real-time transmission system has experienced a different format due to COVID19 pandemic outbreak and the need for transmission to be realized in an online format. We developed our non-dedicated system by independently purchasing video, audio, computer equipment and used it for the first time in the realization of ZASINK 2020 in a completely online format with multiple participants from different countries at the same time streaming on the zoom platform (Figures 4 and 5).

Conclusion

By presenting the experience and development of the telemedicine system for the needs of ZASINK Congress, we have shown the possibilities of upgrading and adaptability of the telemedicine system in accordance with the needs and requirements.

Figures 4 and 5. Online zoom platform streaming

References

1. Starren JB, Nesbitt TS, Chiang MF. "Telehealth". Biomedical Informatics: computer applications in health care and biomedicine, edited by Shortliffe EH, Cimino JJ, Springer London: 2014;4:541-560.
2. Al-Shorbaji N. The World Health Assembly Resolutions on eHealth: eHealth in Support of Universal Health Coverage. Method Inform Med 52(06);463-466.
3. World Health Organization 2016. Global diffusion of eHealth: making universal health coverage achievable: report of the third global survey on eHealth. WHO Document Production Services, Geneva, Switzerland.
4. Bashshur RL, Shannon GW, Krupinski EA et al. National telemedicine initiatives: essential to healthcare reform. Telemed J E Health 2009;15(6):600-610.
5. Khanndpur RS. Telemedicine, technology and applications (mHealth, TeleHealth and eHealth). Asoke K, PHI Learning Private Limited, Delhi 2017;(5).
6. World Health Organization 2000. Health information systems development and strengthening : guidance on needs assessment for national health information systems development. World Health Organization, Geneva, Switzerland.
7. Crico C, Renzi C, Graf N et al. mHealth and telemedicine apps: in search of a common regulation. Ecancer Med Sci 2018;12:853.
8. Aitken M, Lyle J. Patient adoption of mHealth. Report by the IMS Institute for Healthcare Informatics. Sep 2015.
9. Kovačević M, Šutić V, Brašanac-Ogrizović M. Upotreba informaciono-komunikacionih tehnologija u Republici Srbiji, 2020. Edited by Panović M, Ogrizović-Brašanac M. Republički zavod za statistiku, Beograd, Srbija: 2020;10-12.

Sažetak

Razvoj telemedicine u Srpskoj interventnoj kardiologiji

Aleksandar Jolić[1], Milan Nikolić[1], Vladimir Mitov[1], Dragana Adamović[1] ,Marko Dimitrijević[1], Milan Nedeljković[2]

[1]Odeljenje invazivne kardiologije, Zdravstveni centar Zaječar, [2]Klinika za kardiologiju, Univerzitetski Klinički centar Srbije; Medicinski fakultet, Univerzitet u Beogradu

*Telemedicina (telemedicine) uključuje upotrebu savremene tehnologije, naročito dvosmerne interaktivne audio/video komunikacije, računara i telemetrije radi pružanja zdravstvenih usluga udaljenim pacijentima ili radi olakšanja razmene podataka između lekara primarnog nivoa zdravstvene zaštite i specijalista koji su fizički udaljeni. Gruba podela sistema koji se koriste u telemedinske svrhe (ne ulazeći u sisteme za e-zdravlje kao **širi** pojam), vrši se na sisteme tzv namenskog karakatera , ili anglosaksonski „proprietary" sisteme, kao i nenamenske sisteme.*

Prvi ZASINK realizovan je novembra 2015. Godine korišćenjem Polycom sistema (HDX 7000) uvideli smo da je sistem u mogućnosti da preko vrlo jednostavne i malo zahtevne internet tehnologije (tzv SIP protkolom, uz vrlo mali zahtev po pitanju internet protoka od samo 4/4 Mbit/s) ovog puta u lokalnoj mreži izvrši ono što nam je u tom trenutnu bilo dovoljno. Postavljanjem daljinski kontolisane kamere sistema (Eagle Eye kamera), sa mogućnostu kontrole sa prostog daljinskog upravljača i mogućnošću unosa više prememorisanih položaja kamere, u samu salu, eliminisali smo potrebu za složenom, glomaznom TV opremom, kao i potrebu za prisustvom paramedinskog osoblja u samoj angio sali. Svim ovim prenošen je video zapis perkutanih procedura u realnom vremenu iz angio sale sa fizičke udaljenosti od oko 500 metara. Pri tome je na prijemnom kraju koriščen drugi Polycom videokonferencijski sistem. ZASINK 2017.održan je u hotelu „Jezero" na Borskom jezeru, te je tada ova oprema prvi put uspešno korišćena za prenos van lokalne mreže. Istom opremom realizovani su i kongresi BASICS i "Meet the future od Serbian cardiology" 2018. i SYNERGY 2019. godine.

Dalje unapređivanje sistema prenosa u realnom vremenu je doživeo drugačiji format pojavom COVID pandemije i potrebom da se prenos realizuje u on line formatu. Razvili smo svoj nenamenski sistem samostalnom nabavkom video, audio, kompjuterske opreme i prvi put ga koristili u realizaciji ZASINK 2020. u potpuno onlajn formatu sa više učesnika iz različitim država u isto vreme streaming-om na Zoom platfromu.

Prikazom iskustva i razvoja telemedicinskog sistema za potrebe ZASINK kongresa pokazali smo mogućnosti nadogradnje i adaptibilnost telemedicinskog sistema u skladu sa potrebama i zahtevima.

Ključne reči: *telemedicina, videkonferencija, Polycom namenski, nenamenski, ZASINK*

Srce i krvni sudovi 2021; 40(4): 268-273

Original article

Transradial versus transfemoral access for female patients who underwent primary PCI in STEMI: Two years follow-up data from acute STEMI interventional registry

Oliver Kalpak, Hristo Pejkov

University Clinic of Cardiology, Interventional Cardiology, Skopje, Macedonia

Abstract

Background: Female patients possess a higher risk for poorer outcome in ST segment elevation myocardial infarction (STEMI). There is possibility that transradial access (TRA) for primary percutaneous coronary intervention (PPCI) could provide better outcome than transfemoral access (TFA) in female patients with STEMI.

Methods: During access transition period from 2008 to 2010, 418 female patients (out of 1808 patients) underwent PPCI for acute STEMI. The registry recruited all-comers patients with acute STEMI. Major bleeding and vascular access site complications, death rates, and overall MACE rates (composite of death, stroke, re MI and TVR) after 2 years follow-up were compared between TRA and TFA.

Results: TRA for PPCI was performed in 261 patients and 157 underwent TFA PPCI. The 30-days and 1 year mortality rates were lower in TRA compared to TFA (6.9 vs. 14.6%, p = 0.009, and 8.8 vs. 15.3%, p.0.032, respectively). After 2 years follow-up, the overall MACE rates were similar (26.4% vs. 31.2%, p.0.17). The major bleeding and particularly major vascular access site complications were more favorable for TRA than TFA (4.4 vs. 14%, p< 0.001, and 2.7 vs. 10.8 %, p.0.001, respectively).

Conclusion: Transradial access for primary PCI in female patients provides less bleeding and lower incidence of vascular access site complications, and better early clinical outcome in acute STEMI.

Key words transradial approach; female gender; STEMI

Background

Ischemic heart disease causing acute coronary syndrome, particularly acute myocardial infarction, is the leading cause of death in many countries.[1-2] It has been projected that it still be the main cause of mortality and disability over the year of 2020.[3] In patients presenting with acute ST elevation myocardial infarction (STEMI), primary percutaneous coronary intervention (PPCI) is recommended reperfusion therapy when it can be performed in a timely fashion by experienced operators in a PCI-capable center.[4] Various ways have been introduced to get better outcome for patients who underwent PPCI, such as optimal antiplatelet therapies and improvement procedural related aspects. Access site is an important procedural aspect related to the successful of a PCI procedure, including PPCI. Transfemoral access (TFA), which was previously used as the main access for PCI, has been associated with substantially higher risks of bleeding and transfusions than transradial access (TRA) as shown in a recent meta-analysis.[5] Recent randomized trial, as well as data registry from our center, revealed that TRA has less bleeding events, lower vascular access site complication and better clinical outcome compared with transfemoral access (TFA) in STEMI patients undergoing PPCI in acute STEMI.[6-8]

Female gender has been known to possess poorer outcome in STEMI.[9] Previous studies have also reported worse in-hospital and long-term mortality of women undergoing elective PCI by TFA.[10-11]. On the other hand, radial approach may decrease access site–related bleeding in women undergoing elective PCI.[11]

Anatomically, radial artery is more superficial, and close proximity to the radial bone, which makes haemostasis easier than TFA.[12] Whether these benefits of TRA would result in better clinical outcomes for female patients who underwent PPCI in the setting of acute STEMI remains to be defined.

In the present study, we sought to compare the outcome of female patients who underwent PPCI in acute STEMI with TRA and the default TFA.

Methods

Study population

With the growing evidences on the favorability of TRA in PCI, our center has completely transformed from default TFA to TRA in 2011. During the transitional period of default TFA to TRA within the year of 2007 to 2010, there were 1808 patients underwent PPCI in acute STEMI included in the registry. The registry recorded all

Address for correspondence: Dr Oliver Kalpak, University Clinic of Cardiology, Interventional Cardiology, Vodnjanska 17, Skopje, Macedonia

comers with acute STEMI, irrespective of clinical presentation. All procedures were done by 7 interventional cardiologists who have experienced in performing PCI both by TFA or TRA. All of these operators have performed at least 100 elective PCI's by TRA before commenced to do PPCI by TRA. Decision to do the PCI by TFA or TFA was left to the discretion of the operator. The results of cohort in overall 1808 patients in the registry have been published recently.[8]
We selected all female patients recruited in the registry for the present study. The data of each case was immediately entered to the registry by the operator after the procedure. The data of registry was open to the health administration and public health insurance administration

Interventional Procedures

The detail of PPCI procedure has been described elsewhere.[8] Briefly, a modified Seldinger technique was performed to obtain TFA. After local infiltration with 3-5ml 2% lidocaine, the femoral artery was punctured with a 17G needle and 0.035 inch guide-wire, followed by 10 cm 6Fr introducer sheath placement. On TRA, radial artery was accessed after local infiltration with 1 – 1.5 ml 2% lidocaine, using counter puncture technique with a 20G plastic iv cannula and 0.025 inch mini guide-wire of 45 cm, and followed by 6Fr hydrophilic introducer sheath placement. The spasmolytic cocktail of 5 mg verapamil was administered through the sheath.

To perform PPCI, standard guiding catheters (such as: Judkins, EBU, Amplatz, etc), mostly 6Fr and sometimes 5Fr, for both TRA and TFA were used. The guide-wires for PCI, mostly Balance Middle Weight (Abbott Vascular,USA) and some hydrophilic wires, were used as indicated by the operator's judgment. The stents choice was left to the operator's consideration. Flow of infarct-related artery was evaluated before and after the PPCI procedure using the TIMI (Thrombolysis in Myocardial Infarction) score. Manual thrombus aspiration was performed in the cases with high thrombus burden. PCI only on the infarct related artery was done with the main goal to reach the TIMI-3 flow.[13]
Standard medications in acute STEMI were given to all patients. These include aspirin (300 mg followed by 100 mg/day indefinitely), clopidogrel (loading dose 600 mg followed by 75 mg/day for at least 1 year), as well as intravenous bolus of unfractioned heparin (100 IU/kg), When required, abciximab was given intracoronary or intravenous bolus of 0,25 mg/kg followed by 0,125µg/kg/min infusion for 12 hours. After completion of PCI, weight adjusted dosage protocol of heparin infusion was continued for 24 hours or 12 hours protocol of abciximab. No fibrinolytic agent was used during PPCI.
Sheath removal for TFA was done after 3-4 hours from the sheath insertion, and haemostasis was achieved by manual compression of 15-20 minutes followed by prolonged weight compression placement. Patient must remain in bed thereafter, with restricted mobility, in the following six hours (9-10 hours in total from the sheath insertion). On TRA, the arterial sheath was removed immediately after the procedure. Haemostasis was achieved by a simple bandage compression or TR band (Terumo, Japan). The simple bandage compression was applied with 4-6 small elastic bands compressing the radial artery at the puncture site. The TR band was applied by inflating 13-15 ml of air at the puncture site. The TR band was gradually deflated each hour after procedure, and removed after four hours. Patients had no mobility restriction after the procedure.

Study end-points

The primary end-points for this study purposes were cardiovascular death and the major cardiovascular events (MACE) within 30 days, 1 year, and 2 years. The MACE was composite of death, stroke, re-MI, and target vessels revascularization. The secondary end-points consist of: major vascular access complications, major bleedings, and non-CABG bleeding in 30 days. Comparison of baseline- and procedural characteristics between TRA and TRA were also evaluated. The baseline characteristics include variables of demography and clinical presentations. Meanwhile procedural-related characteristics during PPCI consist of variables: culprit lesions, diseased vessels, IABP use, time-frame related, and contrast use.
Cardiovascular death includes cardiovascular related death, includes: death in acute MI, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, and death due to other cardiovascular causes.
Major vascular access complications was defined as any access site related hemorrhage requiring red blood cell transfusion, delayed hospital discharge or requiring a surgical vascular repair.[14]
Major bleeding was defines as overt clinical bleeding (or documented intracranial or retroperitoneal hemorrhage) associated with a drop in hemoglobin of 5 g/dL, or in hematocrit of 15%.[15]
Term of Non-CABG bleeding refers to a major bleeding, which not related to any CABG procedures.[16] Time from onset to intervention was defined as time from onset of acute STEMI symptoms to the start of PPCI. Meanwhile, procedural time was defined as time from puncture arterial access until the time of guide-catheter pulled out from the sheath at the end of PPCI.

Statistical Analysis

Continuous variables were expressed as mean $\pm$ standard deviation for normally distributed data and median with the range (maximum-minimum) for data that not fitting with normal distribution. Comparison of continuous data between TRA and TFA was performed with Student t-test or Mann-Whitney U test when appropriate. Categorical variables were presented in numbers and percentage, and comparison between the groups was done by Chi-square test or Fischer exact test. Clinical outcome of PPCI between TFA and TRA group was analyzed by univariate log-regression and reported as odds ratio (OR) with the corresponding 95% confidence intervals (CI), calculated for the endpoints. Survival

curves were constructed using Kaplan-Meier techniques, and comparisons were made by Mantel-Cox log rank test. The significances were considered for $p < 0.05$.

Results

During transitional period of default TFA to TRA for PCI within the year of 2007 to 2010, there were 1808 patients with acute STEMI underwent PPCI. Among them 418 women who were included in the present study. Their median age was 62 years old (range of 30-86 years). The PPCI was done 261 (62.4%) with TRA, and 157 with TFA (37.6 %). Major cardiovascular risk-factors were similar between the groups of TRA and TFA. History of major comorbidities such as previous: PCI, CABG, and renal insufficiency were not significantly different between the two groups. Clinical presentations in the time of PPCI includes: anterior MI, cardiogenic shocks, and time of MI onset to intervention were also similar between the groups of TRA and TFA. Those baseline characteristic comparing TRA and TFA is listed in the Table 1.

Table1. Baseline Characteristics

Variables	TRA (N=261)	TFA (N=157)	P
Risk factors & Comorbidities			
Age, years	62.4 ± 10.5	60.3 ± 9.6	0.05
Diabetes	89 (34.1%)	56 (35.7%)	0.41
Hypertension	181 (69.3%)	108 (68.8%)	0.49
Dyslipidemia	99 (37.9%)	63 (40.1%)	0.36
Smoker	89 (34.1%)	50 (31.8%)	0.35
Family history	40 (15.3%)	22(14.0%)	0.41
Previous PCI	14 (5.4%)	12 (7.6%)	0.23
Previous CABG	0 (0.0%)	1 (.0.6%)	0.37
Previous CHF	4 (1.5%)	5 (3.2%	0.21
Renal insufficiency	3 (1.1%)	2 (1.3%)	0.62
Clinical Presentations:			
Anterior MI	130 (49.8%)	72 (45.9%)	0.25
Cardiogenic Shock	8 (3.1%)	7 (4.5%)	0.31
Onset to Intervention, min	230 (40-960)	254 (30-870)	0.24

During PPCI procedure, the most frequent culprit lesion finding was in the left anterior descending (LAD) coronary artery both in the group of TRA (49.8%), and in TFA (45.9%). The culprit lesion in the bifurcation part of coronary arteries was more frequent in the TRA group (18.8%) than in the TFA (8.9%). Angiographic results during PPCI showing associated coronary disease such as diseases in the LM trunk and the multivessel involvement were not different between TRA and TFA. Most of patients were with pre-interventional TIMI flow 0-1 in the culprit lesion that was not significantly different in TRA (74.7%) and TFA (79.0%). The overall PPCI procedures resulted in similar goal, in term of percentage of culprit vessels reaching TIMI 3 flow, between TRA and TFA (91.2% vs. 91.7%). The time-frame related during PPCI includes: door to balloon time, procedural time, and fluoroscopic time were not different between the groups of TRA and TFA. The PPCI by TRA consumes significantly least amount of contrast than in the TFA ($p < 0.001$). The overall PPCI procedural-related characteristics in TRA and TFA are presented in the Table 2.

Table 2. Procedural-related characteristics

Variables	TRA (N =261)	TFA (N=157)	P
Culprit lesions			
LAD	130 (49.8%)	72 (45.9%)	0.24
LCx	32 (12.3%)	15 (9.6%)	0.24
RCA	95 (36.4%)	70 (44.6%)	0.06
Bifurcation	49 (18.8%)	14 (8.9%)	< 0.01
Diseased vessels			
With LM disease	7 (2.7%)	5 (3.2%)	0.49
Multivessel	149 (57.1%)	80 (51.0%)	0.13
IABP use	1 (0.4 %)	2 (1.3%)	0.32
Reperfusion parameter			
Baseline flow TIMI 0-1	195 (74.7%)	124 (79.0%)	0.19
Post procedural TIMI 3	238 (91.2%)	144 (91.7%)	0.50
Time-frame related			
Door to balloon time, min	40 (12-610)	40 (12-187)	0.15
Procedural time, min	22 (7-50)	22 (7-45)	0.96
Fluoroscopic time, min	7 (4-37)	8 (4-41)	0.07
Contrast used, ml	100 (45-300)	136 (46-350)	< 0.001

Primary and Secondary end-points

At 30 days after PPCI, the death incidence of female patients with acute STEMI was significantly lower in TRA group than TFA (6.8 vs. 14.6%, p=0.012). At 1 year and 2 years follow up, the cumulative incidence of death in TRA still lower in TRA than TFA (8.8 vs. 15.3%, p=0.045, and 9.2 vs. 16.6%, p=0.027, respectively). When these death incidences combined with stroke, re-MI, and target vessels revascularization into MACE, we found significantly lower MACE at 30 days and 1 year in TRA group compared to TFA (9.2 vs. 15.9%, p=0.041; and 16.1 vs. 22.9%, p=0.042). The MACE at 2 years follow up, although showing lower percentage number in TRA group, but not significantly different than TFA (26.4 vs. 31.2%, p=0.179). The Odd ratio's (95% CI) for all events are less than 1 suggesting favorable result of TRA than TFA.

Major vascular access bleeding complications during PPCI was lower in TRA than TFA (2.7 vs. 10.8%, p=0.001). The non-access related bleeding , in 30 days showed lower trend in TRA compared to TFA (3.4 vs. 5.7%, p=0.227), and overall Major bleeding was again significantly lower in TRA group (4.4 vs. 14.0 %, p=0.001). The Odd ratio's (95% CI) for all events are less than 1 suggesting favorable result of TRA than TFA which clearly indicated favorability of TRA than TFA. The overall primary and secondary end-points are shown in Table 3.

Table 3. Primary and secondary end-points

Study End-points	TRA (N=251)	TFA (N=157)	OR (95 % CI)	P
Primary end-points :				
30 days Death	18 (6.9%)	23 (14.6%)	0.43 (0.22-0.85)	0.012
1 year Death	23 (8.8%)	24 (15.3%)	0.53 (0.29-0.98)	0.045
2 years Death	24 (9.2%)	26 (16.6%)	0.51 (0.28-0.92)	0.027
30 days MACE	24 (9.2%)	25 (15.9%)	0.54 (0.29-0.97)	0.041
1 year MACE	42 (16.8%)	38 (24.2%)	0.60 (0.37-0.98)	0.042
2 years MACE	69 (26.4%)	49 (31.2%)	0.82 (0.51-1.22)	0.336
Secondary end-points :				
Major Vascular Access Bleeding	7 (2.7%)	17 (10.8%)	0.21 (0.10-0.64)	0.001
Major Non-Access Bleeding	9 (3.4%)	9 (5.7%)	0.59 (0.23-1.51)	0.270
Major Bleeding Overall	12 (4.4%)	22 (14.0%)	0.27 (0.13-0.58)	0.001

Survival analysis

Kaplan-Meier estimates of MACE at 30 days in women who underwent PPCI in the present study revealed a significantly higher cumulative survival in TRA compared to TFA (p=0.009). The survival curves at 1 year and 2 years, although juxtaposed still observed, but were not significantly different between TRA and TFA (p=0.06 and p=0.209, respectively). The survival curves at 30 days, 1 year, and 2 years are shown in Figure 1.

Discussion

The present study revealed real world findings regarding early- and 2 years clinical outcome of female patients who underwent PPCI in acute STEMI by TRA compared to TFA. We found lower cumulative mortalities in 30 days, 1 year, and 2 years in TRA than TFA. The overall MACE at 30 days and 1 year were lower in TRA, but not significantly different in 2 years, compared to TFA. We also revealed lower 30 days major vascular access complications, major bleeding, and non CABG bleeding in female patients who underwent PPCI by TRA compared to TFA. The Kaplan-Meier curves of MACE rate up to 2 years follow-up indicated that TRA may improve early survival, particularly at 30 days after PPCI in women, but this benefit of events free survival rate was not lasting after 1 year and beyond over TFA.

Female gender has been associated with worse outcome in acute coronary syndrome, particularly in acute STEMI. Previous studies in patients with STEMI treated by primary angioplasty in the era of default TFA showed that women were associated with higher mortality rate in comparison with men, mainly because of their high-risk profile and angiographic features.[17] Among those risks, women reportedly have smaller vessels profile than men. Other report also revealed women have greater left ventricular filling pressures compared with men, independent of age, hypertension, and infarct size in acute STEMI.[18] Indeed, female gender with acute STEMI who undergoing PPCI can be considered as a high risk group. Certainly, a better management, both medications and procedural related, will always be required to improve outcomes in this demographic entity.

In patients undergoing both diagnostic catheterization and PCI by TFA, previous reports have demonstrated that female gender is a powerful predictor of bleeding and vascular complication [19–20] In the setting of elective PCI, women have been known with higher risk of bleeding than men. Study in a large number gender difference in PCI concluded that despite the improvement in procedural safety, female gender continues to be associated with a -2-fold risk of bleeding and vascular complications compared with men.[21] Over the last decade, several procedural-related improvements have been introduced, still, female gender remained associated with a higher risk of local bleeding and hematomas.[22] Taken together, female gender possess a worse outcome in acute STEMI and also poorer outcome in PCI by default TFA related to vascular complications compared to men.

Bleeding and vascular complications events would affect clinical outcome after PCI, including death and overall MACE.[19,20,23] In present study of women who underwent PPCI by TRA, we found lower bleedings and vascular complications than TFA. This may explain better early outcome and MACE rate of TRA over TFA in those pa-

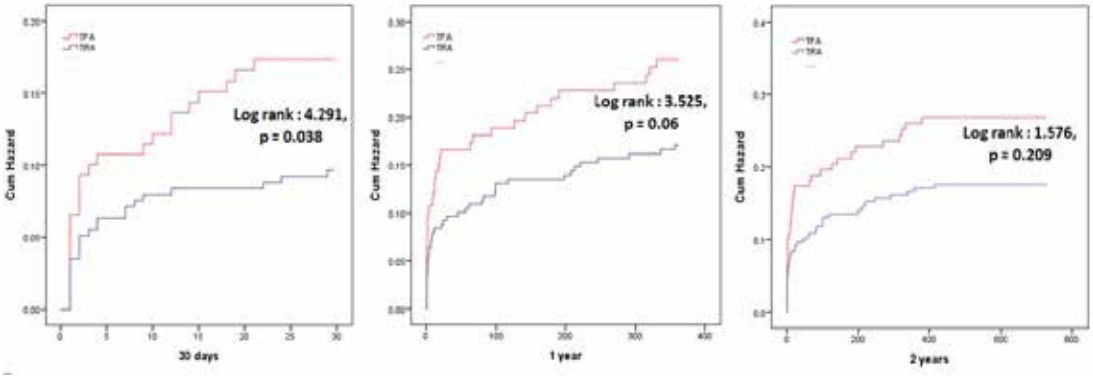


Figure 1. Kaplan-Meier MACE curves at 30 days, 1 year, and 2 years, comparing TRA and TFA

tients as shown in the results. Thus, TRA for PPCI in female with acute STEMI provides benefits of improving clinical outcome, particularly early outcome, by reducing risk of bleeding and vascular complications if the procedure performed by TFA. These findings suggest applying default TRA for women undergoing PPCI when it is required.

Favorability of TRA over TFA in PCI has been reported in previous studies.[5,24-25] Most of available evidences reported less risk of bleeding and vascular access complications. Some other studies also have reported lower death rate and MI by TRA compared to TFA.[5,24] Reduction of bleedings and vascular access complications would reduce these adverse events. However recent large cohort study of more than 2 million PCI procedures in US reported that TRA for PCI is underused in patients at high risk of bleeding, such as: older patient, women, and patient presenting with ACS. [24] The study suggested wider adoption of TRA for PCI, particularly in high risk patients, may present opportunity to potentially improve overall PCI safety. Our study represented very high risk group, which is female and in acute STEMI. Favorable results in safety and efficacy of this study advocate for using default TRA over TFA in PPCI for this very high risk group.

Less contrast use is other advantage of applying TRA over TFA in PPCI, as seen in the result. This aspect may also beneficial to reduce the risk of contrast-induced nephropathy. In the patient's side, the TRA for PCI certainly more convenient for them, better mobilization and they may discharge earlier after procedural. Nevertheless, applying TRA as default access for PCI requires sufficient learning curve for both operator as well as the entire paramedic in a cath lab. As experience of our center, the transitional period of default TFA to TRA for PCI, including for PPCI, lasted around 3 years from 2007 to 2010. As for today, as high as 99 % procedures of coronary interventions, both elective and in acute coronary syndrome cases, and even carotid angioplasty are done through radial access in our center.[8,26-27] We found TRA is a safe, less bleeding and lower vascular access complications, and provides better clinical outcome after PCI, including in high risk groups such as female patients and those with acute STEMI.

Study limitation

The data of present study was taken from a registry, not a randomized study. However, this study represents a real world result, since we included all-comers female patients with STEMI who underwent PPCI during certain period. Baseline characteristics of risk factors, co-morbidities, as well as clinical presentation were not significantly different between TRA and TFA groups as seen in Table 1.

Conclusions

Transradial access for female patients who underwent primary PCI in acute STEMI provides better early outcome than transfemoral access, and reveals less major vascular access complications and major bleedings. These study suggest favorability of transradial as the default interventional access, including for PPCI, in female patients over the transfemoral access.

References

1. Morrow DA. Cardiovascular risk prediction in patients with stable and unstable coronary heart disease. Circulation 2010; 121:2681-2691.
2. Hochman JS, Tamis JE, Thompson TD, et al. Sex, clinical presentation, and outcome in patients with acute coronary syndromes. Global use of strategies to open occluded coronary arteries in acute coronary syndromes. N Engl J Med 1999;341:226-232.
3. Murray CJL, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global burden od disease study. Lancet 1997;349(9064):1498-1504.
4. 2013 ACCF/AHA Guideline for the management of ST-elevation myocardial infarction. J Am Coll Cardiol 2013;61(4):e78–140
5. Bertrand OF, Belisle P, Joyal D. et al. Comparison of transradial and femoral approaches for percutaneous coronary interventions: A systematic review and hierarchical Bayesian meta-analysis. Am Heart J 2012;163:632-648.
6. Généreux P, Mehran R, Palmerini T, et al. Radial access in patients with ST-segment elevation myocardial infarction undergoing primary angioplasty in acute myocardial infarction: the HORIZONS- AMI trial. EuroIntervention 2011;7:905–916.
7. Romagnoli E, Biondi-Zoccai G, Sciahbasi A, et al. The RIFLE-STEACS (Radial Versus Femoral Randomized Investigation in ST-Elevation Acute Coronary Syndrome) study. J Am Coll Cardiol 2012;60:2481-2489.
8. Kedev S, Kalpak O, Antov S, et al. Complete transitioning to the radial approach for primary percutaneous coronary intervention: A real world single center Registry of 1808 consecutive patients with acute ST elevation myocardial infarction. J Invasive Cardiol 2014;26:475-482.
9. Sadowski M, Gasior M, Gierlotka M, et al. Gender-related differences in mortality after ST-segment elevation myocardial infarction: a large multicenter national registry. Euro Intervention 2011;6(9):1068-1072.
10. Peterson ED, Lansky AJ, Kramer J, et al. Effect of gender on the outcomes of contemporary percutaneous coronary intervention. Am J Cardiol 2001;88:359-364.
11. Agostoni P, Biondi-Zoccai GG, de Benedictis ML, et al. Radial versus femoral approach for percutaneous coronary diagnostic and interventional procedures; systematic overview and meta-analysis of randomized trials. J Am Coll Cardiol 2004;44:349-356.
12. Kedev S. Transradial Primary Percutaneous Coronary Intervention. Intervent Cardiol Clin 2015;4: 167–177.
13. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. N Engl J Med 1985;312:932-936.
14. Verheugt FW, Steinhubl SR, Hamon M, et al. Incidence, prognostic impact and influence of access and nonaccess site bleeding in percutaneous coronary intervention. J Am Coll Cardiol Intv 2011;4:191-197.
15. Cannon CP, Braunwald E, McCabe CH, et al. The Thrombolysis in Myocardial Infarction (TIMI) trials: the first decade. J Interv Cardiol 1995;8:117–135.
16. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation 2011;123:2736-2747.
17. De Luca G, Suraprana H, Dambrink JH, et al. Sex-related differences in outcome after ST-segment elevation myocardial infarction treated by primary angioplasty: data from the Zwolle Myocardial Infarction study. Am Heart J 2004;148(5):852-856.
18. Drever RP, Beltrame JF, Neil C, et al. Cardiac hemodynamics in men versus women during acute ST-segment elevation myocardial infarction. Am J Cardiol 2013 ;112(2):143-149.
19. Dripped G, Berger PB, Mehilli J, et al. Periprocedural bleeding and 1-year outcome after percutaneous coronary interventions: appropriateness of including bleeding as a component of a quadruple end point. J Am Coll Cardiol 2008;51: 690–697.

20. Budaj A, Eikelboom JW, Mehta SR, et al; OASIS 5 Investigators. Improving clinical outcomes by reducing bleeding in patients with non-ST-elevation acute coronary syndromes. Eur Heart J 2009;30:655-661.
21. Ahmed B, Piper WD, Malenka D. Significantly improved vascular complications among women undergoing percutaneous coronary intervention. Circ Cardiovasc Intervent 2009;2:423-429.
22. Marcos HT, Bertrand OF, Cabau JR, et al. Impact of female gender and transradial coronary stenting with maximal antiplatelet therapy on bleeding and ischemic outcomes. Am Heart J 2009; 157:740-745.
23. Eikelboom JW, Mehta SR, Anand SS, et al. Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006;114:774-782.
24. Feldman DN, Swaminathan RV, Kaltenbach LA, et al. Adoption of radial access and comparison of outcomes to femoral access in percutaneous coronary intervention. Circulation 2013;127:2295-2306.
25. Kijmenei F, laarman GHL, Odekerken D, et al. A Randomized comparison of percutaneous transluminal coronary angioplasty by the radial, brachial and femoral approaches: the Access study. J Am Coll Cardiol 1997;29:1269-1275.
26. Kedev S, Kalpak O, Antov S, et al. The prevalence and outcomes of transradial percutaneous coronary intervention for acute coronary syndrome. Analysis from the single-centre ISACS-TC Registry (International Survey of Acute Coronary Syndrome in Transitional Countries) (2010–12)
27. Kedev S, Mann T. Transradial carotid angiography and stenting. Interven Cardiol Clin 2014;3:21-35.

Srce i krvni sudovi 2021; 40(4): 274-276

Case report

Ergospirometry in the assessment of functional significance of myocardial ischemia

Ivana Nedeljkovic[1,2], Vojislav Giga[1,2], Ana Djordjevic Dikic[1,2], Nikola Bošković[2], Milorad Tešić[1,2], Milan Dobrić[1,2], Marina Ostojic[1,2], Milan Nedeljković[1,2], Marko Banović[1,2], Olga Petrovic[1,2], Ivana Jovanović[2], Branko Beleslin[1,2]

[1]Medical faculty, University of Belgrade, [2]Cardiology Clinic, University Clinical centre of Serbia

Sažetak It has been shown that the ECG exercise stress test (ET) has low sensitivity and this limitation is successfully overcome by combinations with imaging techniques (stress echocardiography (ESE), nuclear medicine, magnetic resonance). Despite improved accuracy in the detection of myocardial ischemia and segmental wall motion analysis, these combinations cannot precisely determine the significance of functional impairment. Thus, the application of ergospirometry significantly improved the sensitivity of ECG ET. In addition to the fact that the most important parameters of CPET are peak myocardial oxygen consumption (PeakVO2) and assessment of ventilatory function, there are specific CPET markers. Significant myocardial ischemia (> 10% of the left ventricular myocardium i.e 3 segments) leads to significant dyssynergia (hypo or akinesia) inducing transient decrease in the ejection fraction. We can detect this point as a plateau (flattening) of the oxygen pulse (VO2/HR) as a consequence of decreased stroke volume and, also, the inadequate increase in VO2 despite the increase of the workload load. These markers appear after echocardiographic changes, and before ECG changes and chest pain on the ischemic cascade of events. We presented a case of a patient with complete left branch block and suspected coronary heart disease who showed typical changes on CPET, and a significant narrowing of LAD on coronary angiography. We used combined stress echocardiography with CPET (ESE-CPET) to confirm ischemia.

Ključne reči Ergospirometry, myocardial ischemia, combined stress echocardiography cardiopulmonary exercise test

Introduction

The application of ergospirometry (CPET) with expiratory gas analysis significantly improved the sensitivity of ECG ET[1,2,3]. The most important features of the CPET are objective determination of the maximal functional capacity - peak myocardial oxygen consumption (PeakVO2) and assessment of ventilatory function. However, significant transient myocardial ischemia (> 10% of the left ventricular myocardium i.e 3 segments) leads to significant dyssynergia (hypo or akinesia) inducing significant decrease in the ejection fraction which can be presented as a plateau or flattening of the oxygen pulse (VO2/HR) and, also, the inadequate increase in VO2 despite the increase of the workload load. These markers appear after echocardiographic changes, and before ECG changes and chest pain on the ischemic cascade of events[1,4] .

Case Report

A 50 years-old male patient, was referred for CPET due to exertional dyspnea. He had well controlled arterial hypertension, and hypercholesterolemia. Physical examination confirmed a normal finding in the heart and lungs and 12 - channel electrocardiogram (ECG) showed sinus rhythm, and image of left bundle branch block (LBBB) (Figure 1).

CPET test (maximal treadmill Bruce with breath-by-breath analysis) lasted 11 minutes and was terminated in the presence of CPET sigs of ischemia accompanied by severe dyspnea. Working efficacy reached the plateau and was decreased (8 ml/kg/min) accompanied by the oxygen pulse flattening followed by increase after the end of the test. (Figure 2). Ventilatory parameters were normal. As we are referral ESE center this test was combined with the ESE with echocardiograpic assessment before and after the test (wall motion analyses and examination of the diastolic function because of unexplained dyspnea. We detected the exercise induced hypokinesia of the distal segments of septum nad inferior left ventricular wall. Diastolic functin was preserved as mitral E to mitral anular è ratio was 9.

Coronary angiography showed 90% diameter stenosis of mid LAD and RCA minor luminal narrowing and was treated by percutaneous coronary intervention with the stent implantation.

Address for correspondence: Ivana Nedeljković, School of Medicine, University of Belgrade, Cardiology Clinic, University Clinical Center of Serbia, Višegradska 26, 11000 Belgrade, E-mail: ivannanedeljkovic@yahoo.com

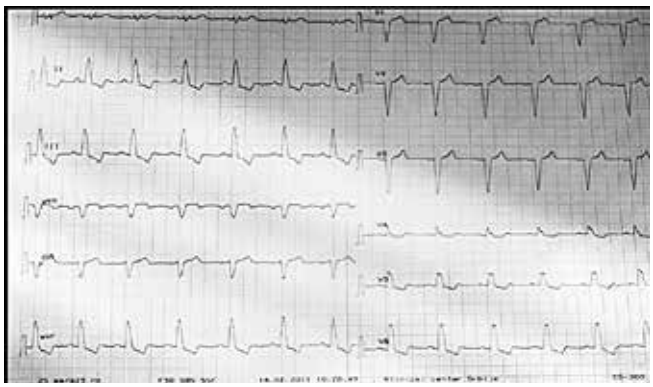


Figure 1. The resting ECG with the left bundle branch block in patient with unexplained dyspnea and chest pain

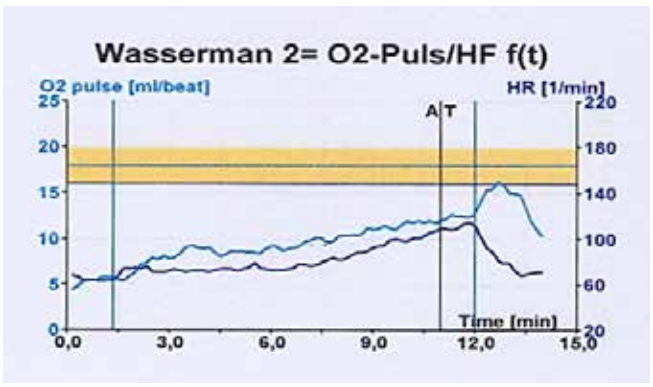


Figure 2. Oxygen pulse flattening in the presence of mzocardial ischemia folloed by increase in stroke volume at recovery
O2 pulse- oxygen pulse; HR- heart rate; AT- anaerobic threshold;

Disscusion

CPET is a well-accepted physiologic evaluation technique in patients with heart failure and in individuals presenting with unexplained dyspnea on exertion[4]. Several variables obtained during CPET, including oxygen consumption relative to heart rate (VO2/HR or O2-pulse) and work rate (VO2/Watt) were shown to be a sensitive marker of myocardial ischemia[1,2,3]. It provides a physiologic quantification of the work rate, heart rate and O2 uptake at which myocardial ischemia develops. The potential value of adding CPET with gas exchange measurements is likely to be of great value in diagnosing and quantifying both overt and asymptomatic myocardial ischemia and the improvement of ischemic threshold with optimal medical treatment[3]. The presence of functionally significant ischemia can be due to macro-vascular disease or microvascular disease or both[4]. We present the patient with the LBBB and unexplained dyspnea who demonstrated the CPET signs of myocardial ischemia and significant obstructive heart disease on coronary angiography.

CPET has the great potential to quantify the global ischemic burden regardless of mechanism and location of lesions[4]. parameters of CPET are peak myocardial oxygen consumption (PeakVO2) and assessment of ventilatory function, when it comes to ischemia, there are specific CPET markers. Significant myocardial ischemia > 10% of the left ventricular myocardium i.e 3 segments) leads to significant dyssynergia (hypo or akinesia) inducing transient decrease in the ejection fraction.

Bellardineli et al.[2] prospectively studied CPET in 1265 consecutive subjects without documented coronary heart disease. As compared with ECG parameters, sensitivity and specificity, were all improved significantly. Patients with both peak VO2 > 91% of predicted VO2 max and absence of VO2-related signs of myocardial ischemia had no evidence of CAD in 100% of cases.

As oxygen pulse (VO2/HR) is O2 volume from O2 delivered to tissue (SV) during every heart beat (ml/beat), it represents SV, respectively. During the transient exercise induced myocardial ischemia, we can detect the O2 pulse flattening, while reduced SV can be compensated by additional increase in arterio-venous O2 difference (C(a-v)O2), to maintain O2 supply on submaximal workload[4]. The interesting sign appears immediately after test termination immediately after test termination. In normal subjects O2 pulse decreases, while but in the presence of ischemia it increases paradoxically (as a consequence of improved SV at recovery period)[1,4]. Also the working efficacy - slope ΔVO2/Δwork rate (rate of O2 expenditure during linear increase of workload. It shows cardiovascular response and muscle efficiency and should be linear and constant (10 ml/min/WATT). ΔVO2/ΔWR slope is normal at lower workload and decreases in the presence of significant myocardial ischemia. ECG changes and angina can be absent[3,4]. Our patient had the LBBB and did not have chest pain during the test in the presence of CPET markers of myocardial ischemia.

These markers appear after echocardiographic changes, and before the appearance of ECG changes and chest pain on the ischemic cascade of events[1,2,3].

However, De Lorenzo et al, did not find the significant relationship between abnormal O2 pulse curve and myocardial ischemia defined by scintigraphy[5]. This can be overcome by the combination of CPET with ESE integrating the diagnostic power offered by both the tools[6]. This combined approach has been demonstrated to be valuable for diagnosing several cardiac diseases, including heart failure with preserved or reduced ejection fraction, cardiomyopathies, pulmonary arterial hypertension, valvular heart disease and coronary artery disease[6]. Using combined ESE-CPET in our case, we confirmed the presence of segmental wall motion abnormalities during the CPET.

Conclusion

Simultaneous flattening in ΔVO2/ ΔWR and O2 pulse with increasing work rate confirms the development of myocardial ischemia during exercise (Table 1). We also showed the potential of ESE - CPET in the detection of asymptomatic myocardial ischemia, as well as in persons with ECG changes that make interpretation difficult (LBBB, myocardial hypertrophy).

Table 1. CPET and exercise test parameters in patients with and without myocardial ischemia[4]

PRIMARY CPET VARIABLES		
O2 pulse trajectory	% Peak VO2 pred.	ΔVO2/ΔW trajectory
Cont. rise and possible plateau approaching maximal exertion	≥ 100%	Continual rise throughout ET
Early and sustained plateau	75 - 99%	Early and sustained plateau
	50-75%	
Continual rise throughout ET	<50%	Continual rise throughout ET
STANDARD EXERCISE VARIABLES		
Haemodynamics	EKG	
Rise in systolic BP during ET	No sust. arrh, ectopic foci, and/or ST changes and/or in recovery	
Flat systolic BP response during ET	Altered rhythm, ectopic foci, and or ST changes and/or in recovery: did not lead to test termination	
Drop in systolic BP during ET	Altered rhythm, ectopic foci, and or ST changes and/or in recovery: led to test termination	
SYMPTOMS		
Lower extremity muscle fatigue	Angina	Dyspnea

ΔVO2 – Change of the myocardial oxygen consumption; ΔW – change of the workload; ET- exercise test;

References

1. Bellardinelli B, et al. Exercise induced myocardial ischemia detected by cardiopulmonary exercise testing. Eur Heart J 2003; 24;1304-1313.
2. Belardinelli R, Lacalaprice F, Tiano L, et al. Cardiopulmonary exercise testing is more accurate than ECG-stress testing in diagnosing myocardial ischemia in subjects with chest pain. Int J Cardiol 2014;174(2): P337-342.
3. Chaudhry S, Ross A, Wasserman K, et al. Exercise-induced myocardial ischemia detected by cardiopulmonary exercise testing. Am J Cardiol 2009; 103:615-619.
4. Guazzi M, Adams V, Conraads V, et al. Clinical recommendations for cardiopulmonary exercise testing data assessment in specific patient populations. Circulation 2012;126:2261-2274.
5. De Lorenzo A, Da Silva AD,. Castro Souza FD, et al. Value of the oxygen pulse curve for the diagnosis of coronary artery disease Physiol Res 2018;67:679-686.
6. Nedeljkovic I, Banovic M, Stepanovic J, et al. The combined exercise stress echocardiography and cardiopulmonary exercise test for identification of masked heart failure with preserved ejection fraction in patients with hypertension. Eur J Prev Cardiol 2016;23:71-77.

Sažetak

Ivana Nedeljkovic[1,2], Vojislav Giga[1,2], Ana Djordjevic Dikic[1,2], Nikola Bošković[2], Milorad Tešić[1,2], Milan Dobrić[1,2], Marina Ostojic[1,2], Milan Nedeljković[1,2], Marko Banović[1,2], Olga Petrovic[1,2], Ivana Jovanović [2] ,Branko Beleslin [1,2]

[1]Medicinski fakultet , Univerzitet u Beogradu, [2]Klinika za kardiologiju, Univerzitetski klinički centar Srbije

Pokazano je da samostalni EKG test fizičkim opterećenjem (TFO) ima nisku senzitivnost u otkrivanju miokardne ishemije i ovo ograničenje se uspešno prevazilazi kombinacijama sa viziualizacionim tehnikama (stres ehokardiografija, nuklearna medicina, magnetna rezonanca). Uprkos tome, ove kombinacije ne mogu precizno odrediti funkcionalni značaj oštećenja. Tako je primenom ergospirometrije sa analizom ekspiratornih gasova značajno poboljšana senzitivnost EKG TFO. Pored činjenice da su najvažniji parametri CPET-a vršna potrošnja kiseonika (PeakVO2) i procena ventilacione funkcije, kada je ishemija u pitanju, postoje specifični markeri. Značajna ishemija miokarda (> 10% miokarda leve komore, tj. 3 segmenta) dovodi do takvih ispada kinetike (hipo ili akinezije) koji izazivaju značajno smanjenje ejekcione frakcije i pad udarnog volumena. Ovu tačku možemo detektovati kao prerani plato kiseoničnog pulsa (VO2/HR) i, takođe, neadekvatnog povećanja VO2 uprkos povećanju opterećenja. Ovi markeri se javljaju nakon ehokardiografskih promena, a pre pojave EKG promena i bolova u grudima na ishemijskoj kaskadi događaja. Mi smo predstavili slučaj bolesnika sa kompletnim blokom leve grane i sumnjom na koronarnu bolest srca koji je tokom CPET pokazao tipične promene , a na koronarografiji značajno suženje LAD. Ishemija je potvrđena istovremenom primenom CPET i stres ehokardiografije (ESE-CPET).

Ključne reči: ergospirometrija, ishemija miokarda, kombinovana stres ehokardiografija sa kardiopulmonalnim testom

Srce i krvni sudovi 2021; 40(4): 277-281

Case report

Distal ulnar palmar approach to treat bifurcation stenosis of the left main (Medina 1.1.0) with Culotte technique

Oktaj Maksudov, Farhat Fouladvand

UMHAT Heart and Brain, Bulgarian Cardiac Institute, Burgas, Bulgaria, San Carlo Clinic,Italy

Abstract

Background: Female patients possess a higher risk for poorer outcome in ST segment elevation myocardial infarction (STEMI). There is possibility that transradial access (TRA) for primary percutaneous coronary intervention (PPCI) could provide better outcome than transfemoral access (TFA) in female patients with STEMI.

Methods: During access transition period from 2008 to 2010, 418 female patients (out of 1808 patients) underwent PPCI for acute STEMI. The registry recruited all-comers patients with acute STEMI. Major bleeding and vascular access site complications, death rates, and overall MACE rates (composite of death, stroke, re MI and TVR) after 2 years follow-up were compared between TRA and TFA.

Results: TRA for PPCI was performed in 261 patients and 157 underwent TFA PPCI. The 30-days and 1 year mortality rates were lower in TRA compared to TFA (6.9 vs. 14.6%, p = 0.009, and 8.8 vs. 15.3%, p.0.032, respectively). After 2 years follow-up, the overall MACE rates were similar (26.4% vs. 31.2%, p.0.17). The major bleeding and particularly major vascular access site complications were more favorable for TRA than TFA (4.4 vs. 14%, p< 0.001, and 2.7 vs. 10.8 %, p.0.001, respectively).

Conclusion: Transradial access for primary PCI in female patients provides less bleeding and lower incidence of vascular access site complications, and better early clinical outcome in acute STEMI.

Key words transradial approach; female gender; STEMI

Introduction

Angiography and percutaneous coronary intervention (PCI) through arteries of the upper extremities is superior to femoral approach, and is on a rise due to less bleeding, easier practice of hemostasis, more patient convenience, shorter procedure time, lower cost imposed to patients and health system, and shorter period of hospitalization.[1-4] In addition, patients will sooner restore their routine physical activity in case of an upper extremity approach. Artery size, anatomical variations, arterial loop, hypoplasia, radial artery occlusion (RAO), previous RA harvesting for coronary artery bypass graft (CABG), and so like are the most troublesome issues with trans-radial approach.[2,5,6] In other words, this approach is not always successful with obligatory shift to other routes.[7] Although many investigators have shown that complications of trans-ulnar approach are rather equal to trans-radial approach, and the latter is suggested as an alternative to trans-radial approach,[5,8-10] but trans-ulnar approach has also its own difficulties and limitations; so, more innovative routes with lower complications and higher patient and operator convenience are strongly warranted. In this our clinical case, we presented new access in the upper limb at more distal points in contrast to conventional approaches, i.e.trans-palmar approach. Clinical case from our daily practice of haevily obese patient with unstabile angina. Angyography shown multivessel disease with distal LM disease involving the ostium of LAD and significant in-stent restenosis in prox LCx (Medina 1,1,0). Heart team's conclusion was CABG. Patient refused cardiosurgery and accepted angioplasty. The size of LAD and LCx were approximarely the same with no acute side branch angle, so we decided to do a Cullotte IVUS guided LM stenting by right distal ulnar palmar approach.

Case presentation

A 77 years/old female patient , heavily obese (BMI 44.4 kg/m^2) had following risk factors: diabetes mellitus insulin dependent, hypertension, metabolic syndrome, and positive family history of CAD. She had following coronary procedures: November 2018 - 2 DES implanted in proximal and mid circumflex artery (LCx) due to STEMI, and in December 2018 long tapered DES was implanted in mid left anterior descending artery (LAD). She was symptomatic for a few days prior to hospitalization. ECG showed sinus rhythm, heart rate of 72/min, negative T wave in leads I, aVL, and V5-V6 (Figure 1). Laboratory results were normal. Echocardiography showed large hypokinesia and dilatation of left ventricle with EF 38% (Figure 2). Angiography (Figure 3) was performed through 6F right ulnar approach, due to radial artery occlusion from previous angioplasty. The conclusion was

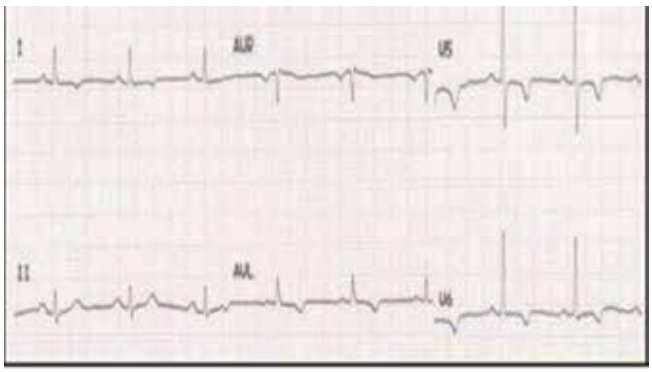


Figure 1. ECG

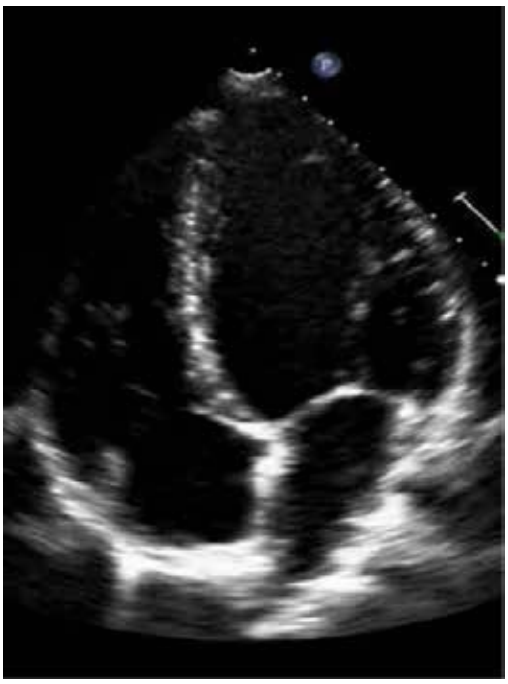
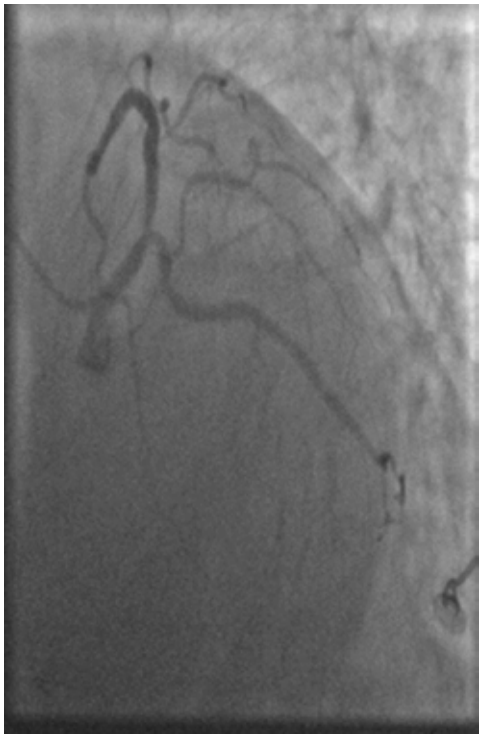
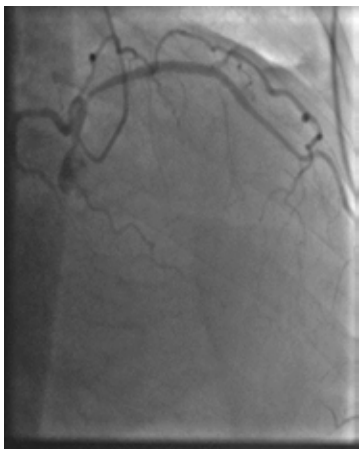


Figure 2. Echocardiography





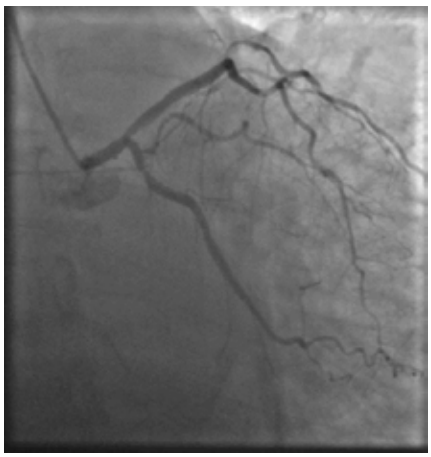


Figure 3-5. LM - distal 60% stenosis involving ostium of LAD (Medina 1,1,0)
LAD - significant ostioproximal stenosis with patent stents in mid LAD, LCx - 80% in-stent restenosis in proximal LCx

multivessel disease with distal LM disease involving the ostium of LAD, and significant in-stent restenosis of proximal LCx (Medina 1,1,0).

Due to radial occlusion and morbid obesity, the procedure was performed by distal ulnar palmar approach with sheathless GC PB 3.5/7.5Fr (Figure 6). The size of LAD and LCx were approximarely the same with no acute side branch angle, so we decided to proceed with a Cullotte technique with IVUS guided left main (LM) stenting. Two "workhorse" wires BMW were placed in LAD and LCx. IVUS in the LM showed significant 60% stenosis in distal segment with minimal luminal area (MLA) of 5.1mm^2, considered to be also functionally significant (Figure 7).

We did pre-dilatations with two semicompliant balloons (3.0x20mm) towards LAD and LCx and kissing balloon inflation with the same ballons (Figure 8). Then, we deployed DES 3.5/24 mm from LM towards LCx (Figure 9). After rewiring LAD and dilatation of the struts toward LAD with non-compliant balloon 2.5/15mm (Figure 10), we implanted DES 3.5/32mm from LM towards LAD, with proximal overlap (Figure 11). We performed proximal optimization with non-compliant balloon (4.0/12 mm, Figure 12), and recrossed the stent to LCX and perform final kissing balloon with 2 non-compliant balloons (3.75/18mm, Figure 13) with final proximal optimization with the same balloon use for the first optimization. The final results showing optimal angiographic result (Figure 14), and nicely opened stents with stent boost technique (Figure 15).

Final IVUS (Figure 16a-c) was done and showed following dimensions: LM (minimal diameter 3.8mm; maximal diameter 4,2mm2, luminal area 12.2 mm^2), LAD (minimal diameter 3.7mm; maximal diameter 4.1 mm2, luminal area 11.4 mm^2), and Cx (minimal diameter 3.7mm; maximal diamater 3.7mm, luminal area 9.3mm^2). The final appearance after PCI of the palmar region is presented in Figures 17a and b.

One, 3 and 6 months after revascularization the patient was completely symptom free. Control echocardiogra-

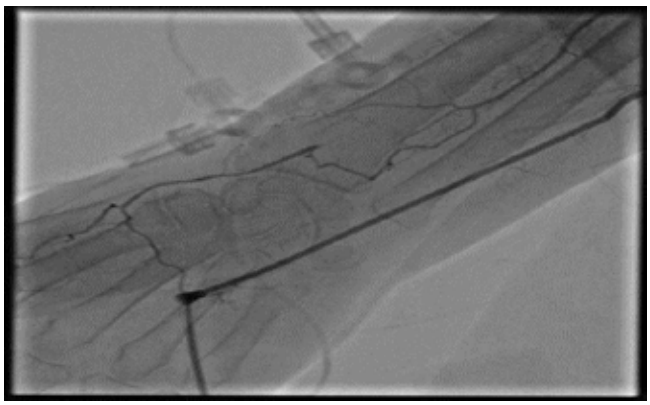


Figure 6.

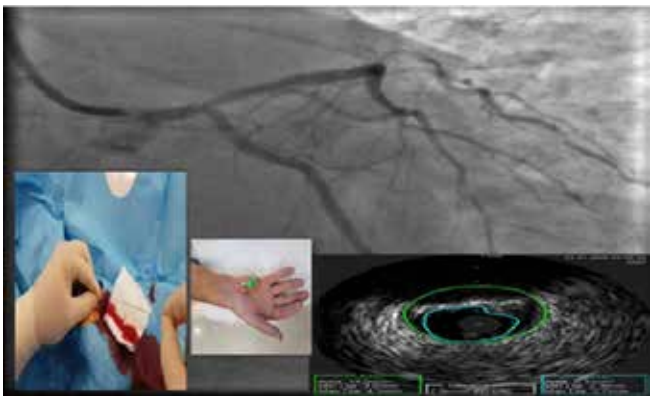


Figure 7.

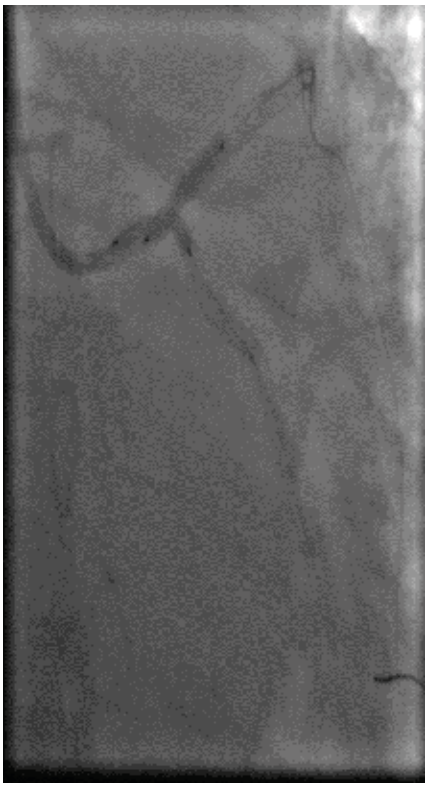


Figure 8.

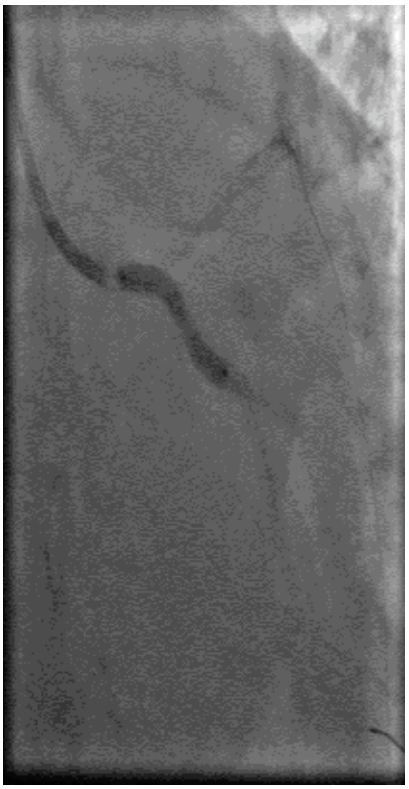


Figure 9.

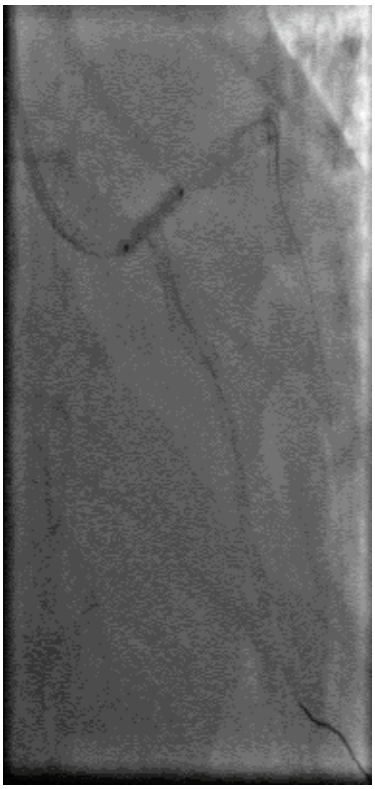


Figure 10.

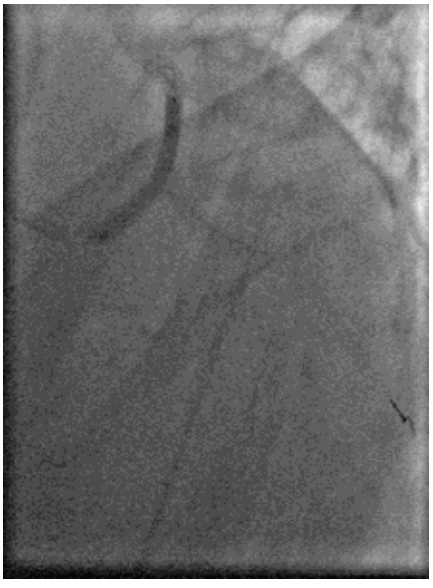


Figure 11.

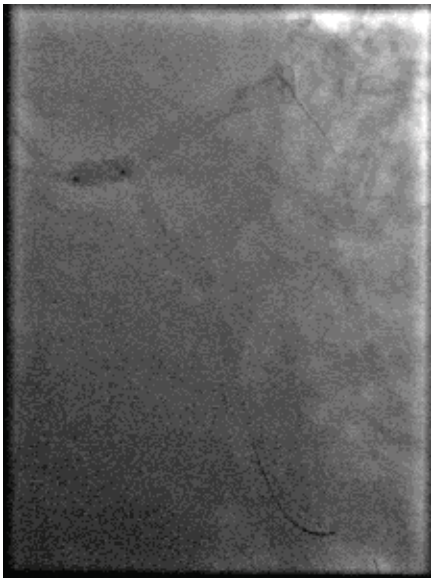


Figure 12.

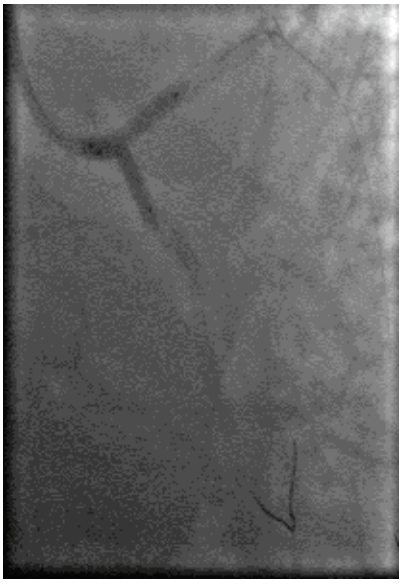


Figure 13.

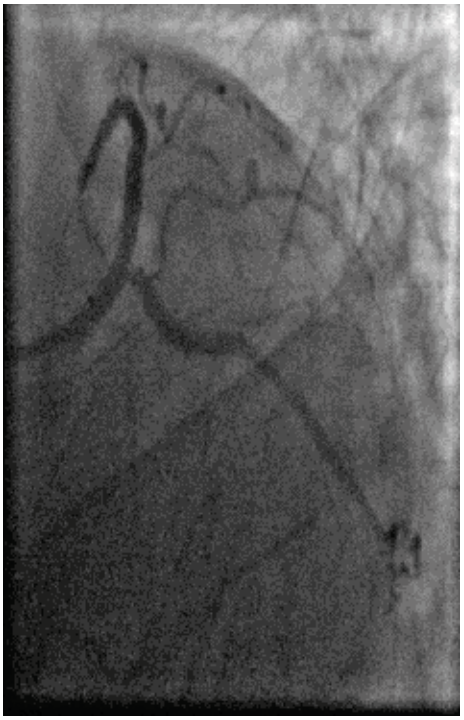


Figure 14.

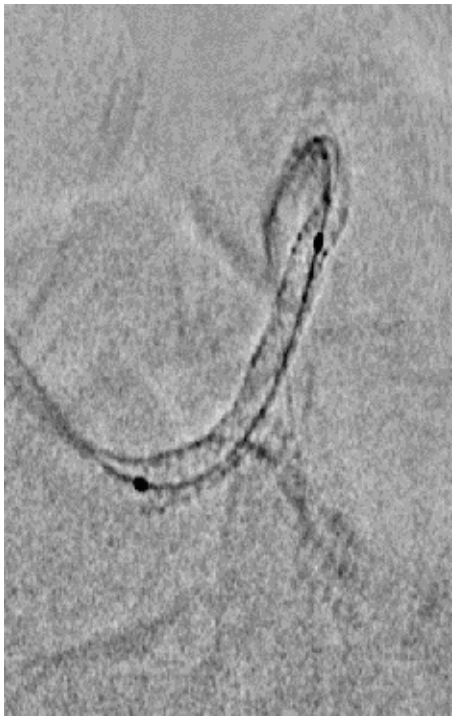


Figure 15.

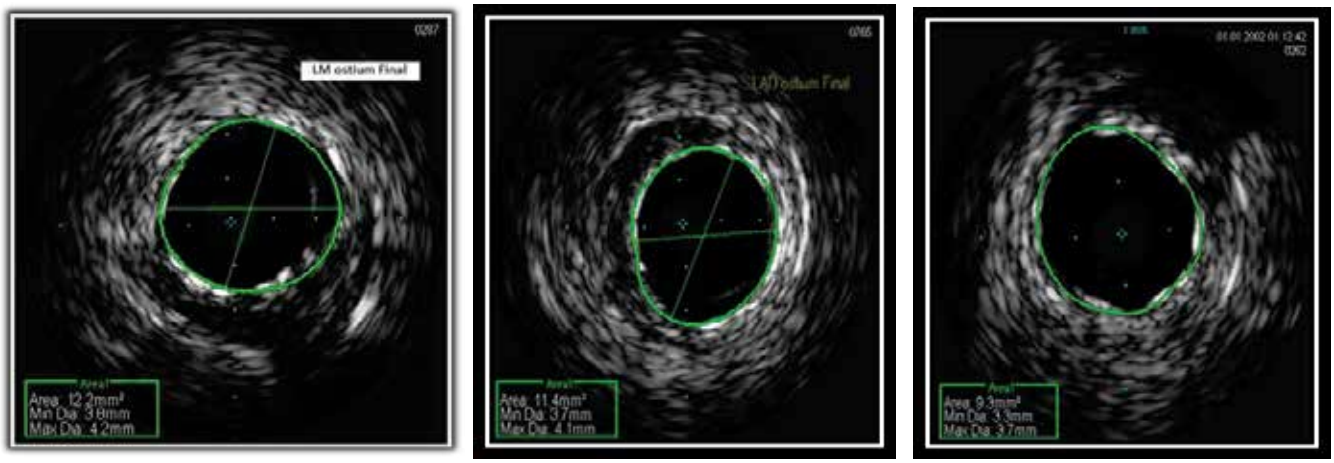


Figure 16. a-c

Figure 17. a, b

phy showed improvement of ejection fraction to 48%. One year follow-up is in progress.

Discussion

As a conclusion, although this new innovative approach could be suggested safe, feasible, and reliable to be used for coronary angiography and/or angioplasty with low complications, but they are at their early stages with about a follow-up period of 1-6 months; so more researches based on large clinical trials are recommended to be conducted in forthcoming months and years. Distal ulnar palmar approach is adequate suitable as the classic approaches/femoral, radial, ulnar, brachial/ for all kind of complex percutaneous interventions.
At the price of a more difficult puncture and risk of access failure, there are possible ergonomic advantages, with lower risk of upstream artery occlusion and shorter hemostasis
In case of complex coronary anatomy indicated for cardiosurgery, and patient refuses operation, PCI/LM/if possible/ is apsolutely indication and adequate solution . Complex Bifurcations remain a challenge for PCI. In such situations, IVUS guidance is preferred. Technique of LM stenting is preferable choise of the operator depending on the anatomy of the vessels and also from the experience of the team, especially experience of the leader of the team, the interventional cardiologyst is crucial for the success of the procedure.

References

1. Liu J, Fu XH, Xue L, Wu WL, Gu XS, Li SQ. A comparative study of transulnar and transradial artery access for percutaneous coronary intervention in patients with acute coronary syndrome. J Interv Cardiol. 2014;27(5):525–30. [PubMed] [Google Scholar]
2. Sallam M, Al-Riyami A, Misbah M, Al-Sukaiti R, Al-Alawi A, Al-Wahaibi A. Procedural and clinical utility of transulnar approach for coronary procedures following failure of radial route: Single centre experience. J Saudi Heart Assoc. 2014;26(3):138–44. [PMC free article] [PubMed] [Google Scholar]
3. Kumar AJ, Jones LE, Kollmeyer KR, Feldtman RW, Ferrara CA, Moe MN, et al. Radial artery access for peripheral endovascular procedures. J Vasc Surg. 2017;66(3):820–5. [PubMed] [Google Scholar]
4. Rao SV, Kedev S. Approaching the post-femoral era for coronary angiography and intervention. JACC Cardiovasc Interv. 2015;8(4):524–6. [PubMed] [Google Scholar]
5. Roghani-Dehkordi F, Hadizadeh M, Hadizadeh F. Percutaneous trans-ulnar artery approach for coronary angiography and angioplasty; A case series study. ARYA Atheroscler. 2015;11(5):305–9. [PMC free article] [PubMed] [Google Scholar]
6. Valsecchi O, Vassileva A, Musumeci G, Rossini R, Tespili M, Guagliumi G, et al. Failure of transradial approach during coronary interventions: Anatomic considerations. Catheter Cardiovasc Interv. 2006;67(6):870–8. [PubMed] [Google Scholar]
7. Dehghani P, Mohammad A, Bajaj R, Hong T, Suen CM, Sharieff W, et al. Mechanism and predictors of failed transradial approach for percutaneous coronary interventions. JACC Cardiovasc Interv. 2009;2(11):1057–64. [PubMed] [Google Scholar]
8. Dahal K, Rijal J, Lee J, Korr KS, Azrin M. Transulnar versus transradial access for coronary angiography or percutaneous coronary intervention: A meta-analysis of randomized controlled trials. Catheter Cardiovasc Interv. 2016;87(5):857–65. [PubMed] [Google Scholar]
9. Gokhroo R, Kishor K, Ranwa B, Bisht D, Gupta S, Padmanabhan D, et al. Ulnar artery interventions non-inferior to radial approach: Ajmer ulnar artery (AJULAR) intervention working group study results. J Invasive Cardiol. 2016;28(1):1–8. [PubMed] [Google Scholar]
10. Roghani-Dehkordi F. Merits of more distal accesses in the hand for coronary angiography and intervention.. Proceedings of the 4th International Cardiovascular Joint Congress in Isfahan; 2016 Nov. 24-25; Isfahan, Iran. [Google Scholar]

Srce i krvni sudovi 2021; 40(4): 282-285

Case report

STEMI with high thrombus burden – two different therapeutic approaches?

Vladimir Zdravković[1,2], Đorđe Stevanović[1,2]
[1]*Department of Interventional Cardiology, Cardiology Clinic, Univesity Clinical Center Kragujevac, Serbia,*
[2]*Faculty of Medical Sciences, University of Kragujevac, Serbia*

Abstract **Introduction**: High thrombus burden (HTB) in patients presenting with acute ST segment elevation myocardial infarction (STEMI) is related to post-operative complications, adverse effects and worse prognosis.
Case reports: We present two similar patients presenting with STEMI, in whom we used two different strategies to cope with HTB after failed manual thrombus aspirations: in the first case we did immediate stenting of infarct related artery (IRA); in the second case, after persisting of no-reflow phenomenon, despite implantation of two stents, we decided to intracoronary administer low-dose alteplase.
Conclusion: Aldo still controversial, evidence suggest that low-dose intracoronary fibrinolytic therapy could be useful in patients presenting with HTB, especially when manual thrombus aspiration have failed. The experience from our center confirms those statements.

Key words intracoronary fibrinolytics, high thrombus burden, ST segment elevation myocardial infarction.

Introduction

Acute ST elevation myocardial infarction (STEMI) most often occurs in the set of atherosclerotic plaque disruption, with the consequent formation of a thrombus that occludes the epicardial coronary artery.[1] According to literature, presence of thrombus can be angiographicaly verified in 91.6% STEMI patients,[2] while the presence of high thrombus burden (HTB) has been reported in 16.4% of cases.[3] While percutaneous coronary interventions (PCI) have revolutionized the treatment of STEMI and have become the standard of care,[4] preforming percutaneous revascularization in the setting of HTB remains challenging.[5]

Quantification of thrombus burden is usually based on Thrombolysis in Myocardial Infarction Risk Scores (TIMI Risk Scores or TS), according to which TS 0 indicates no thrombus is present, and TS 5 indicates definite thrombus, with the largest dimension ≥4 vessel diameters. HTB is defined as TS ≥ 4.[6] However, since there is a high incidence of coronary occlusion in STEMI, in which thrombus burden cannot be adequately assessed due to the absence of antegrade flow distal to occlusion site, *Sianosand colleagues* have proposed a new classification, in which TS 5 is reclassified after wire crossing and/or small balloon (≤ 1.5 mm) is used to recanalize the infarct related artery (IRA).[7]

Presence of HTB in acute myocardial infarction (AMI) patients is related to larger infarction area, left ventricle (LV) function deterioration, greater incidence of post-operative complications and adverse effects, including malignant arrhythmia and heart failure, and worse prognosis in general. [5,8]

This is particularly due to thrombus shifting and distal (micro)embolization, with consequent severe microvasculature obstruction (MVO) causing the no-reflow phenomenon.[9] While angiographic signs of distal embolization occur in 6–18% of cases of primary PCI in STEMI, the true incidence may be much higher. This is demonstrated by retrieval of visible debris in up to 73% patients in studies such as the Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris (EMERALD) trial.[10]

No-reflow phenomenon is associated with worsen LV function, adverse clinical effects and death, and is estimated to occur in at least 10% of STEMI patients.[9,11,12] HTB is considered to be one of the major predictors of the no-reflow phenomenon.[13]

Therefore, several strategies in the setting of HTB have been proposed, including thrombectomy devices, with manual thrombus aspiration as the most commonly used, as well as pharmacological pretreatment. Recently, intracoronary-targeted thrombolysis has become popular and efficient in handling coronary thrombotic lesions.[1,14]

Case report 1

A 55-year-old male was referred to emergency room department due to anginal chest pain, which lasted for 5 hours before admission. ECG showed ST segment elevation > 2 mm in inferior leads with contralateral ST

Corresponding author: Đorđe Stevanović, MD, Department of Interventional Cardiology, Cardiology Clinic, University Clinical Center Kragujevac, Serbia Zmaj Jovina 30, 34 000 Kragujevac, Serbia, Faculty of Medical Sciences, University of Kragujevac, Serbia, Svetozara Markovića 69, 34000 Kragujevac, Serbia Mobile phone: +381606969077;Work phone: +38134505088; Fax: +38134370, E-mail: stevanovic.med@gmail.com

segment depressions, as well as ST segment elevation > 1 mm in V4R lead.
On physical examination, patient was eupnoeic, normotensive. After administering 300 mg of acetylsalicylic acid and 60 mg of Prasugrel, in a hemodynamically stable state, patient was transferred to catheterization lab.
Coronary angiography showed proximally occluded right coronary artery (RCA). (Fig. 1A) After passing the guide wire (GW), TIMI II flow occurred with large residual thrombus burden – TS 4. (Fig. 1B) After several unsuccessful manual thrombus aspirations, DES XiencePro 3,5x38 mm (Boston Scientific, Massachusetts, USA) was primo-implanted in medial RCA at 12 atmospheres (atm), after which DES ResoluteOnyx (Boston Scientific, Massachusetts, USA) 4,5x30 mm was primo-implanted in proxo-medial segment at 12 atm, with overlap. Coronary angiography performed after stent implantations showed migrations of thrombus masses in proximal and distal segment. (Fig. 1C) After implantation of DES Resolute Onyx 4,5x15 mm in ostio-proximal segment at 12 atm and intracoronary administering of nitroglycerin, coronary angiography showed entrapped thrombus masses. (Fig. 1D)
After several postdilations using non-compliant balloons and repeated intracoronary administration of nitroglycerin, final coronary angiogram showed optimal result with TIMI III flow in RCA. (Figure 1E)
In a hemodynamically stable state patient was transferred to Intensive care unit for further treatment. Control coronary angiography, planned 6 months after the procedure, is yet to be conducted.

Case report 2

A 45-year-old male was referred to emergency room department due to chest pain which lasted for 5 hours before admission.ECG showed ST segment elevation > 2 mm in inferior leads with contralateral ST segment depressions. On physical examination, patient was upset, eupnoeic, normotensive. After administering 300 mg of acetylsalicylic acid and 180 mg of Ticagrelor, in a hemodynamically stable state, patient was transferred to catheterization lab.
Coronary angiography showed proximally occluded RCA. After passing the GW, TIMI II flow occurred with large residual thrombus burden – TS gr 4. (Fig. 2-A)
After several unsuccessful manual thrombus aspirations, POBA was performed using the semi-compliant balloon.Control angiogram showed no-reflow phenomenon from medial part of RCA, with presisting thrombus masses in proximal segment. (Fig. 2-B) Procedure was continoued by implanting DES Resolute Onyx3,0x26 mm (Boston Scientific, Massachusetts, USA) in proximal segment, which resulted only in shifting of the starting point of the no-reflow bellow the distal edge of the stent. (Fig. 2-C) We implanted DES Orsiro 3,0x26 (Biotronik, Switzerland)distal segment, after which no-reflow persisted below the crux. (Fig. 2-D) At that point, considering the persisting no-reflow, we decided to intracoronary administer 10 mg of alpteplase in a slow manual infusion over 10 minutes. After restoration of coronary flow and resolution of initial ST segment elevations, we finished the procedure by implanting DES Orsiro 2,5x18 mm (Biotronik, Switzerland) in PL branch. Final angiogram showed optimal result with TIMI III flow. (Fig. 2-E)
In a hemodynamically stable state patient was transferred to Intensive care unit for further treatment. Control coronary angiography, planned 6 months after the procedure, is yet to be conducted.

Discussion

Aldo HTB is recognized to be associated with greater incidence of post-operative complications and adverse effects,[5,8]there are currently no proven recommendations for intervention in this setting. Several strategies have been advocated, including utilization of pharmacological agents and interventional strategies.[1,14] One of the most commonly used interventional strategy is manual thrombus aspiration. However, due to its failure in randomized clinical trials (RCT), the current European Society of Cardiology (ESC) guidelines recommend against the routine use of thrombus aspiration in percutaneous interventions, with consideration in specific cases where there is a HTB and risk of embolization.[4] In both patients, due to significant thrombus burden, we have performed several manual tromboaspirations, but they were without success.
In the first case, after failed thrombus aspirations, we went for immediate stenting of IRA. After implantation of two stents, we witnessed shifting of thrombus masses in both proximal and distal direction, as well as entrapped thrombus masses. This could indicate distal embolization and, possibly, a significant MVO, causing further myocardial injury.[9] Another therapeutic approach in this setting could be deffered stenting, which has showed beneficial effect in several single center experiences and non-randomized trials,[15] as well as in DEFER-STEMI trial (A Randomized Trial of Deferred Stenting Versus Immediate Stenting to Prevent No- or Slow-Reflow in Acute ST-Segment Elevation Myocardial Infarction).[16] However, the largest RCT, the DANAMI 3-DEFER trial (The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: DEFERred stent implantation in connection with primary PCI) failed to show any benefit of deferred stenting on clinical outcomes.[17] Possible alteration that could lead to more beneficial results when deffering the stent implantation could be dosing and duration of GP IIb/IIIa inhibitors, as well as the time period of stenting delay.[15]
In the second case, after failed thrombus aspirations, we have again went for immediate stenting of IRA. After POBA and DES implantation of proximal RCA segment, we witnessed no-reflow phenomenon bellow the distal edge of the stent. In further course of the procedure, and implanting stent in distal segment, no-reflow persisted, only with shifting the starting point of the no-reflow to the lower edge of the distal stent. At that point, we decided to intracoronary administer alteplase in a total dose od 20 mg. Intracoronary thrombolysis has gained some popularity over the past decade, but is still controversial. The

largest meta-analysis about the issue, conducted by S. Agrawal, showed that low-dose intracoronary fibrinolytic therapy is, in general, safe and effective, with a reference that it could be used in the setting of HTB and failed thrombus aspiration.[18] Contrary to that, a RCT - *Effect of Low-Dose Intracoronary Alteplase During Primary Percutaneous Coronary Intervention on Microvascular Obstruction in Patients With Acute Myocardial Infarction*, in which intracoronary alteplase was administered after reperfusion and before stent implantation, showed that adjunctive low-dose intracoronary alteplase given early during the PCI did not reduce MVO.[19] The study included all STEMI patients with impaired blood flow and evidence of thrombus (TS ≥ 2). Therefore, in the authors opinion, the methodology of the study was not adequately set to examine the true clinical use of intracoronary fibrinolytic therapy, for it is reserved, and should be examined, in the setting of HTB and failure of other recommended approaches. In this manner, adequate patient selection and the time point of administering intracoronary fibrinolytic should be defined. Currently, there are two ongoing RCT to evaluate intracoronary low-dose alteplase: the "*Adjunctive Low-dose tPA in Primary PCI for STEMI*" (STRIVE, NCT03335839) study, and "*the Restoring Microcirculatory Perfusion in STEMI"* (RESTORE-MI; ACTRN 12618000778280) trial. Finally, the utility of low-dose intracoronary fibrinolytic was recognized by the actual 2019 Canadian Cardiovascular Society/Canadian Association of Interventional Cardiology Guidelines on the Acute Management of ST-Elevation Myocardial Infarction.[20]

Conclusion

HTB in STEMI patients is challenging, and there is still no strong recommendations to help us safely and effectively lead these procedures.

Manual thrombus aspiration has been downgraded in the actual ESC guidelines and is now not routinely recommended, but reserved to be considered in STEMI patients with HTB. Still, at least in our clinical experience, thrombus aspiration is usually not effective.

Aldo still controversial, evidence suggest that low-dose intracoronary fibrinolytic therapy could be useful in patients presenting with HTB, especially when manual thrombus aspiration have failed. The adequate patient selection and the time point of administering intracoronary fibrinolytic should be defined.

References

1. Kumar V, Sharma AK, Kumar T, et al. Large intracoronary thrombus and its management during primary PCI. Indian Heart J 2020;72:508-516.
2. Guardiola FM, Rossi A, Serra A, et al, on behalf of the Spanish AMI Cath Registry. Angiographic quantification of thrombus in ST-elevation acute myocardial infarction presenting with an occluded infract-related artery and its relationship with outcomes of percutaneous intervention. J Interven Cardiol 2009;22:207-215.
3. D. Fukuda, A. Tanaka, K. Shimada, et al. Predicting angiographic distal embolization following percutaneous coronary intervention in patients with acute myocardial infarction. Am J Cardiol 2003;91:403-407.
4. Ibanez B, James S, Agewall S, et al.2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2018;39:119–177.
5. Ren H, Zheng Y, Hu X, et al. High thrombus burden: a review of mechanisms and treatments. Int J Clin Exp Med 2019; 12:13068-13078
6. Gibson CM, de Lemos JA, Murphy SA, et al. Combination therapy with Abciximab reduces angiographically evident thrombus in acute myocardial infarction: A TIMI 14 substudy. Circulation 2001;103:2550–2555.
7. G. Sianos, M.I. Papafaklis, J. Daemen, et al. Angiographic stent thrombosis after routine use of drug-eluting stents in ST-segment elevation myocardial infarction: the importance of thrombus burden. J Am Coll Cardiol 2007;50:573-583
8. Han YL. Interpretation of 2016 Chinese percutaneous coronary intervention therapy guide. J Clin Military Med Surg 2016;44:441-443.
9. Jaffe R, Charron T, Puley G, et al. Microvascular obstruction and the no-reflow phenomenon after percutaneous coronary intervention. Circulation 2008;117:3152–3156.
10. Stone GW, Webb J, Cox DA, et al. Enhanced myocardial efficacy and recovery by aspiration of liberated debris (EMERALD) Investigators. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. JAMA 2005; 293:1063-1072.
11. Harrison RW, Aggarwal A, Ou FS, et al. Incidence and outcomes of no-reflow phenomenon during percutaneous coronary intervention among patients with acute myocardial infarction. Am J Cardiol 2013;111:178–84.
12. S. Prasad, I. T. Meredith. Current approach to slow flow and no Reflow. Cardiac Interventions Today 2008:43-49.
13. Fajar JK, Heriansyah T, Rohman MS. The predictors of no reflow phenomenon after percutaneous coronary intervention in patients with ST elevation myocardial infarction: A meta-analysis. Indian Heart J 2018;70(Suppl 3):S406-S418.
14. Xiao Y, Fu X, Wang Y, et al. Effects of different strategies on high thrombus burden in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary catheterization. Cor Artery Dis 2019;30:555-563.
15. Pradhan A, Bhandari M, Vishwakarma P, et al. Deferred stenting for heavy thrombus burden during percutaneous coronary intervention for ST-Elevation MI. Eur Cardiol 2021;16:e08.
16. Carrick D, Oldroyd KG, McEntegart M, et al. A randomized trial of deferred stenting versus immediate stenting to prevent no- or slow-reflow in acute ST-segment elevation myocardial infarction (DEFER-STEMI). J Am Coll Cardiol 2014;63:2088-2098.
17. Kelbæk H, Høfsten DE, Køber L, et al. Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial. Lancet 2016;387:2199-206.
18. Agarwal SK, Agarwal S. Role of intracoronary fibrinolytic therapy in contemporary PCI practice. Cardiovasc Revasc Med 2019;20:1165-1171.
19. McCartney PJ, Eteiba H, Maznyczka AM, et al. Effect of low-dose intracoronary alteplase during primary percutaneous coronary intervention on microvascular obstruction in patients with acute myocardial infarction: A randomized clinical trial. JAMA 2019;321:56–68.
20. Wong GH, Welsford M, Ainsworthet C, al. 2019 Canadian Cardiovascular Society/CanadianAssociation of Interventional Cardiology Guidelines on the acute management of ST-Elevation myocardial infarction: Focused update on regionalization and reperfusion. Can J Cardiol 2019;35:107e132

Sažetak

STEMI sa velikim trombom – dva različita dijagnostička pristupa

Vladimir Zdravković[1,2], Đorđe Stevanović[1,2]
[1]Odeljenje za interventnu kardiologiju, Klinika za kardiologiju, Univerzitetski Klinički centar Kragujevac, Srbija, [2]Fakultet medicinskih nauka, Univerzitet u Kragujevcu, Srbija

***Uvod**: Kod pacijenata koji se prezentuju infarktom miokarda sa elevacijom ST segmenta (STEMI), veliko trombotsko opterećenje se dovodi u vezu sa post-opreativnim komplikacijama, neželjenim događajima i gorom prognozom.*
***Prikaz slučaja**: Prezentujemo dva pacijenta sa infarktom miokarda sa ST elevacijom, a kod kojih smo koristili dve različite strategije u cilju rešavanja problema velikog trombotskog opterećenja nakon neuspešne trombo-aspiracije: kod prvog pacijenta odlučili smo se za neposredno stentiranje infarkne arterije; kod drugog pacijent, nakon perzistiranja no-reflow fenomena, čak i nakon implantacije dva stenta, odlučili smo se za intrakoronarnu aplikaciju niske doze alteplaze.*
***Zaključak**: Iako još uvek kontroverzno, dokazi ukazuju na to da bi niske doze intrakoronarno ordiniranih fibrinolitika mogle biti korisne kod pacijenata sa velikim trombotskim opterećenjem, naročito nakon neuspešne trombo-aspiracije. Iskustvo iz našeg centra saglasno je sa tim tvrdnjama.*

***Ključne reči:** intrakoronarna fibrinoliza, veliko trombotsko opterećenje, infarkt miokarda sa ST elevacijom.*

Srce i krvni sudovi 2021; 40(4): 286-289

Case report

Multivessel coronary artery disease – how to reach Heart Team's optimal decision

Ivan Ilic[1,2], Dragan Topic[1]

[1] Institute for cardiovascular diseases Dedinje, Belgrade, Serbia, [2] Medical school, University of Belgrade, Belgrade, Serbia

Abstract We present a case of a 71-year-old gentleman who suffered an inferoposterior ST elevation myocardial infarction treated with thrombolytic therapy where coronary angiography showed triple vessel disease and coronary artery bypass graft (CABG) was suggested. Based on the results of coronary physiology and non-significant values of FFR, Heart team denied revascularization and recommended medical therapy. Data from 11 randomized studies involving more than 11,000 patients comparing PCI to CABG in patients with multivessel disease (MVD) showed pronounced benefit of surgical revascularization in patients with more complex coronary anatomy (higher SYNTAX score) and diabetes. If there is a complex MVD with left main stenosis, the advantage should be given to CABG, as well as in the case of complex MVD and diabetes, while PCI has an advantage in patients with lower SYNTAX score, the ones with advanced age and comorbidities where PCI would offer faster postprocedural recovery. In retrospective analysis by Basman et al., patients subjected to hybrid revascularization techniques had similar mortality as patients that underwent CABG or multivessel PCI and similar incidence of composite outcomes.

Key words coronary artery disease, PCI , CABG

Introduction

We present a case of a 71-year-old gentleman who suffered an inferoposterior ST elevation myocardial infarction that was treated with thrombolytic therapy. Regarding risk factors for atherosclerosis, he used to smoke and received medication for hypertension and dyslipidemia. Coronary angiography was done 18 days after STEMI and a triple vessel disease was seen and coronary artery bypass graft (CABG) was suggested. At admission, he reported occasional chest pain (CCS Class II) and had moderately limited activity (NYHA II). He denies any other illnesses. The echocardiogram showed slightly reduced left ventricular systolic function of with ejection fraction of 45% and akinesia of the basal half of the septum and inferior wall, hypokinesia of the basal half of the posterior wall.

Calculated Synergy Between PCI With Taxus and Cardiac Surgery (SYNTAX) score was 14 and SYNTAX II score predicted equipoise between percutaneous coronary intervention (PCI) and CABG-with 4-year mortality of 6.0% and 7.1% respectively (Figure 1).

Given the low SYNTAX score and previous MI, we opted for coronary physiology – an invasive examination of the significance of narrowing by measuring the fractional flow reserve (FFR), coronary flow reserves (CFR) and index of microcirculatory resistance (IMR) by using coronary wire for pressure and temperature measurement Pressure Wire X (Abbott Vascular, Plymouth, MN, US) and continuous adenosine infusion. The acquired values were as follows: right coronary artery (RCA) FFR 0.84, CFR 1.3, IMR 24.8; circumflex artery (Cx) - FFR 0.95, CFR 2.6, IMR 18.3 and left anterior descending (LAD) FFR 0.90, CFR 1.9, IMR 10.9 (Figure 2).

Based on the results of coronary physiology and non-significant values of FFR with low CFR and borderline IMR values that indicated presence of microvascular dysfunction without significant narrowing of the epicardial coronary arteries, Heart team denied any form of revascularization and recommended maximum medical therapy.

Multivessel coronary artery disease (MVD) and adequate method of revascularization has been a matter of debate in the cardiology community for more than 20 years[1]. The concept of "Heart Team" (HT) was established for multidisciplinary approach to individual patient in order to reach an evidence-based decision regarding the appropriate treatment. In case of a patient with coronary artery disease (CAD), the role of HT is to adequately evaluate anatomical complexity of coronary disease, the possibility of complete revascularization, the assessment of surgical risk of procedure and possible complications of any method of revascularization. The aim of the assessment is to determine the risk – benefit ratio in terms of procedural risks (risk of death, myocardial infarction, heart failure) and periprocedural complications (cerebrovascular event, kidney failure, complications at puncture site, need for transfusion, new onset arrhythmia or wound infection) versus possible benefits in terms of prolongation of life, absence of

Address for correspondence: Clin. Assist Ivan Ilić, Institute for cardiovascular diseases Dedinje, Belgrade, Serbia. E-mail: ivan1ilic@yahoo.com

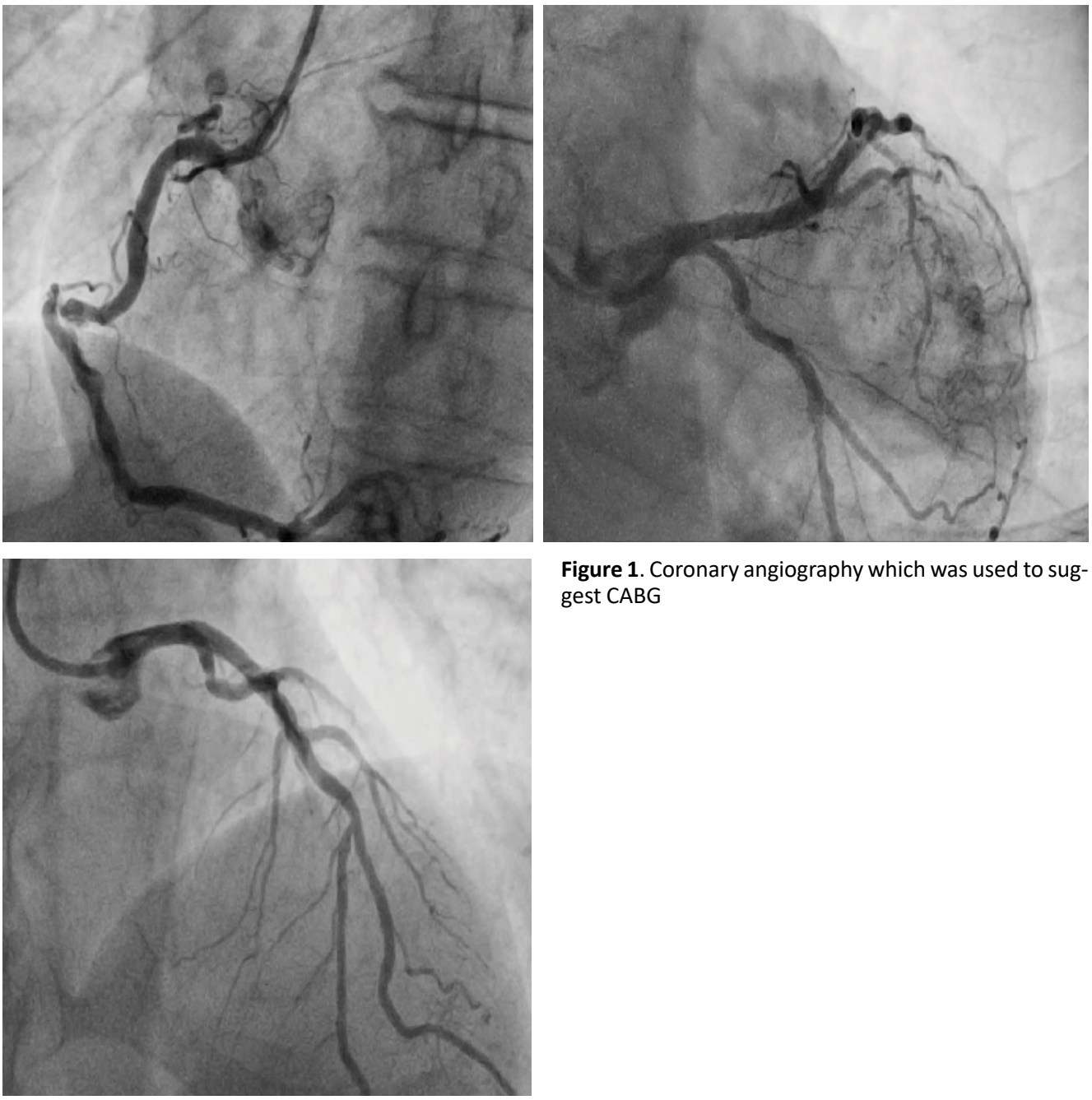


Figure 1. Coronary angiography which was used to suggest CABG

myocardial infarction and improvement in quality of life. The superiority of surgical treatment in case of a patient with MVD has been repeatedly examined in relation to PCI with the development of advanced techniques in interventional cardiology[3]. In daily practice, despite the development in interventional techniques – new generations of drug eluting stents (DES), intravascular imaging (IVUS, OCT), use of coronary physiology (CFR, FFR) and advanced antithrombotic therapies in patients with MVD, the advantage is almost always given to surgical treatment. Current recommendations from European Society of Cardiologists and the European Association of Cardiothoracic Surgeons give absolute advantage to surgical treatment in patients with anatomically complex MVD (high SYNTAX score), while in the intermediate complexity of coronary disease (SYNTAX<22) outcomes, except for myocardial infarction, are similar. If the patient suffers from diabetes, the things are slightly different. Aggregated data from 11 randomized studies involving more than 11,000 patients and comparing PCI to CABG in patients with MVD showed lower five-year mortality rates in those treated with surgical revascularization compared to those treated with PCI (11.5% after PCI to 8.9% after CABG; HR 1. 28, 95% CI 1. 09-1·49;p=0. 0019), including diabetes patients (15. 5% *vs.* 10. 0%; 1. Forty-eight, one. 19-1. 84; p=0. 0004), but not in patients who did not suffer from diabetes (8.7% *vs* 8.0%; 1.08, 0.86–1.36; p=0.49). Additionally, the benefit of surgical revascularization was more pronounced in patients with more complex coronary anatomy (higher SYNTAX score)[4].

A special attention should be devoted to a patient with significant stenosis of left main stem. Previously, available data from randomized studies and meta-analyses showed similar results regarding death, myocardial infarction and repeated revascularization if patients underwent CABG or PCI with DES stent[2,5]. The aforementioned meta-analysis demonstrated similar five-

Figure 2. Measured coronary physiology parameters in RCA, Cx and LAD

year mortality (10.7% after PCI *vs* 10.5% after CABG; p=0·52)[4]. In patients with complex coronary anatomy and LM stenosis, despite fewer patients with these characteristics in randomized studies, surgical treatment would probably be the best treatment option[2,4].

Previous research in this field has been designed before significant advances in interventional cardiology like development of coronary physiology and imaging techniques, which means that, in previously published randomized trials, not many patients had these techniques applied during PCI. Therefore, when choosing revascularization techniques in MVD, complete revascularization of all hemodynamically significant lesions should be sought, either based on anatomical or functional significance obtained using non-invasive or invasive tests to prove it (CFR and FFR)[6].

An interesting alternative is a hybrid approach - combining the surgical revascularization with LIMA (left internal mammary artery) graft and PCI of other lesions in patients with MVD. In retrospective analysis by Basman et al., after propensity matching, patients subjected to hybrid revascularization techniques had similar mortality as patients that underwent CABG or multivessel PCI (5.0% vs. 4.0% vs. 9.0%) and similar incidence of composite outcomes - death, repeated revascularization and myocardial infarction (HCR 21.0% vs CABG 15.0%, P = .36; HCR 21.0% vs PCI 25.0%, P = .60). Despite higher preprocedural SYNTAX score, hybrid revascularization achieved a lower residual score after revascularization than multivessel PCI[7].

Finally, approach to a patient with MVD should be individualized primarily based on the anatomy of coronary artery lesions. If there is a complex MVD with LM stenosis, the advantage should be given to CABG, as well as in the case of multivessel complex MVD and diabetes. In the absence of these characteristics, the severity of CAD should be analyzed while paying respect to patient's preference. The advantage to surgery should be given in patients with very complex lesions (long lesions, chronic total occlusions, calcifications) where percutaneous complete revascularization would be difficult to achieve, while PCI has an advantage in patients

of advanced age, with high risk of cerebrovascular complications, bleeding and infection of the surgical wound, as well as in those where functional capacity is reduced where PCI would offer faster postprocedural recovery.

References

1. Chaitman BR, Rosen AD, Williams DO, et al. Myocardial infarction and cardiac mortality in the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial. Circulation 1997; 96: 2162–70.
2. Neumann FJ, Sousa-Uva M, Ahlsson A, et al; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2019;40(2):87-165.
3. Bhatt DL. CABG the clear choice for patients with diabetes and multivessel disease. Lancet 2018;391(10124):913-914.
4. Head SJ, Milojevic M, Daemen J, et al. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data. Lancet 2018;391(10124):939-948
5. Giacoppo D, Colleran R, Cassese S, et al. Percutaneous coronary intervention vs coronary artery bypass grafting in patients with left main coronary artery stenosis: A systematic review and meta-analysis. JAMA Cardiol 2017;2(10):1079-1088.
6. Gaba P, Gersh BJ, Ali ZA, et al. Complete versus incomplete coronary revascularization: definitions, assessment and outcomes. Nat Rev Cardiol 2021;18(3):155-168.
7. Basman C, Hemli JM, Kim MC, et al. Long-term survival in triple-vessel disease: Hybrid coronary revascularization compared to

Sažetak

Višesudovna koronarna bolest – kako doneti naoptimalniji zaključak kardiohirurškog tima

Ivan Ilić[1,2], Dragan Topić[1]

[1]Institut za kardiovaskularne bolesti Dedinje, Beograd, Srbija, [2]Medicinski fakultet, Univerzitet u Beogradu, Srbija

Predstavili smo slučaj muškarca starog 71 godinu koji je lečen trombolitičkom terapijom nakon akutnog infarkta sa ST elevacijom. Koronarografija je pokazala trosudovnu koronarnu bolest I predloženo je hirurško lečenje bajpas graftom (CABG). Urađena je koronarna fiziologija i na osnovu neznačajnih vrednosti frakcione rezerve protoka (FFR) "Heart team" je indikovao maksimalnu medikamentnu terapiju. Podaci iz 11 studija koje su uključile preko 11000 pacijenata pokazali su korist od CABG-a kod pacijenata sa kompleksnom koronarnom anatomijom (visok SYNTAX skor) i dijabetesom, dok perkutana koronarna intervencija (PCI) ima prednost kod pacijenata sa nižim SYNTAX skorom, starijih sa komorbiditetima, gde PCI nudi brži postproceduralni oporavak. U retrospektivnoj analizi Basmana i saradnika pokazano je da hibridni metod revaskularizacije ima sličnu incidenciju smrti i kompozitnih ishoda kao CABG i višesudovna PCI.

Ključne reči: *koronarna bolest, CABG, PCI*

SPONZORI 7. ZASINK 2021.

GENERALNI SPONZORI

APTUS

HERMES PHARMA

PARTNERI SIMPOZIJUMA

Medtronic

AMICUS
Modern Medicines for All

Boehringer Ingelheim

AstraZeneca

Soul Medical

PHARMASWISS

VICOR

Hemofarm
STADA GRUPA

Abbott

CIS Medical d.o.o.

Удружење здравствених радника Зајечар

SPONZORI SIMPOZIJUMA

BIOTRONIK
excellence for life

KRKA

SANOmed

АЛКАЛОИД
СКОПЈЕ

BAYER
Bayer

SPECIJALISTIČKA INTERNISTIČKA ORDINACIJA
INTERTIM GROUP

mark medical™
empowering healthcare.

TT MEDIK

MEDIJSKI PARTNERI SIMPOZIJUMA

za media

pixArt
web&graphics
studio


SANOFI

OLITOR®

rosuvastatin/ezetimib

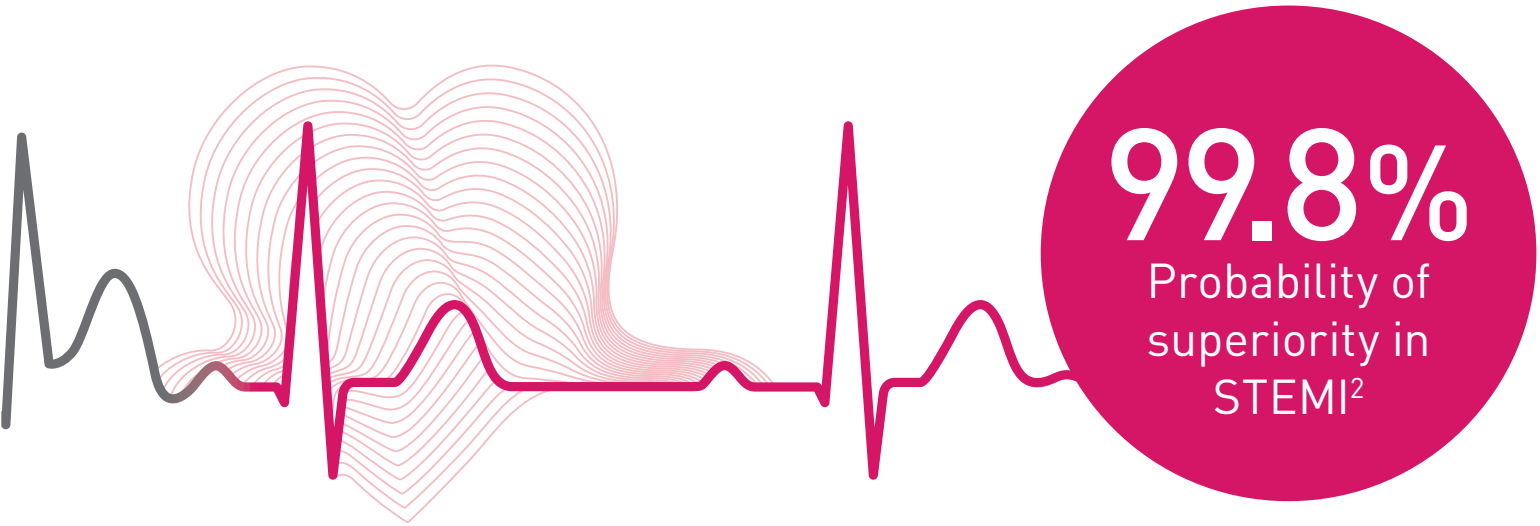
SERVIER

RS-029-OLI-21-LOTH

Orsiro® DES

BIOSTEMI trial: Continued superiority in STEMI at 2 years[1]

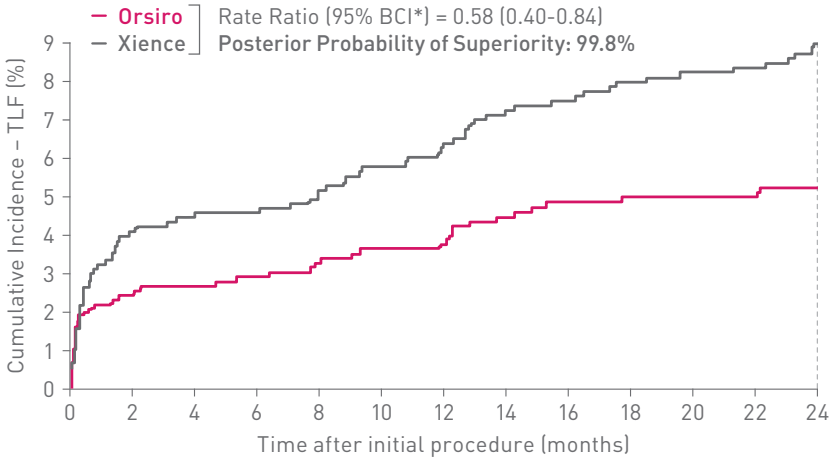
What would you choose for your heart?



99.8%
Probability of superiority in STEMI[2]

Orsiro® DES

BIOSTEMI trial: Continued superiority in STEMI at 2 years[1]



Target Lesion Failure (TLF) rate at 24 months:[3]

5.1% Orsiro

8.1% Xience

*BCI: Bayesian Credible Interval.

1. In comparison to Xience, based on TLF, in the BIOSTEMI trial; 2. Posterior probability of superiority in STEMI in comparison to Xience at 24-months with respect to TLF, based on combined data set of BIOSTEMI and BIOSCIENCE STEMI groups; 3. Pilgrim et al. Biodegradable – versus durable-polymer drug-eluting stents for STEMI. Final 2-year outcomes of the BIOSTEMI trial. J Am Coll Cardiol. Cardiovasc Interven. 2021, doi: 10.1016/j.jcin.2020.12.011. For Indications please see Instructions for Use.

www.orsiro.com

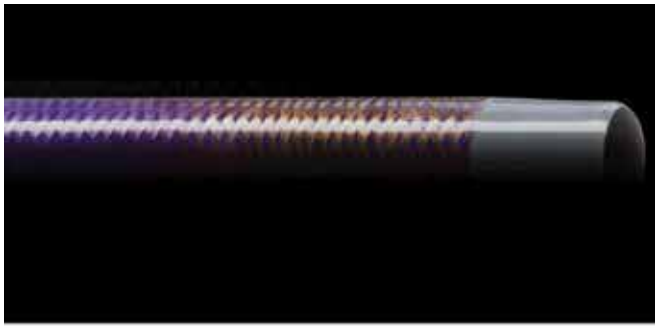
BIOTRONIK
excellence for life

ISO 9001
ISO 14001
OHSAS 18001
ISO/IEC 27001
BUREAU VERITAS
Certification

MEDICOM®
Šabac

mark medical™
empowering healthcare.

Boehringer
Ingelheim



Thinner. Stronger. IDeal.™

Prelude IDEAL™
Hydrophilic Sheath Introducer

Flat wire braiding technology allows our thin wall radial sheath to provide support and kink resistance while maintaining a low profile. There's a reason it's called IDeal.

BENEFITS OF RADIAL ACCESS[1]

- Less bleeding complications
- Quicker ambulation
- Decreased procedure cost
- Enhanced sheath performance

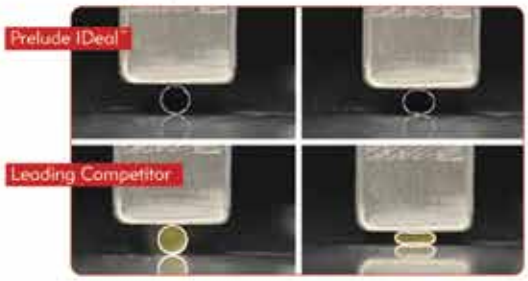
DECREASED INSERTION FORCE*

Requires **15%** less force to insert than leading competitor

Excellent transitions and hydrophilic coating to facilitate smooth insertion

INCREASED COMPRESSION RESISTANCE*

124% more resistant to side wall compression than the leading competitor

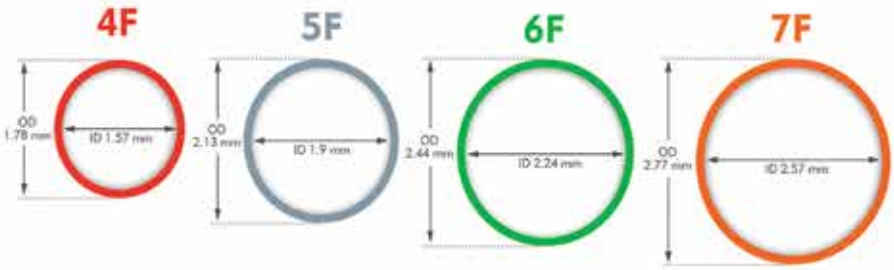


BETTER TORQUE*

Twice the torque than the leading competitor before collapsing

THINNER WALL*

Same outer diameter as leading competitor, but larger sheath body inner diameter



MULTIPLE NEEDLE OPTIONS

Merit Advance® Needle

Two-Part Access Needle

- Thin walled metal cannula
- Flexible, radiopaque catheter
- Smooth catheter-to-needle transition for easy insertion
- Excellent for two-wall access technique
- Up to 17% faster flash back over our leading competitor**
- Up to 17% less insertion force over our leading competitor**
- Visible arrow to help clearly indicate bevel position

MULTIPLE GUIDE WIRE OPTIONS

Kits available with stainless steel spring coil, nitinol or stainless steel mandrel, or plastic jacketed guide wires providing optionsfor your clinical practice.

13% thinner wall with higher resistance to kinking and side wall compression than leading competitor

MERIT MEDICAL™

APTUS d.o.o. Beograd
011/7943-741 011/7943-742


Boston
Scientific
Advancing science for life™


VICOR
VICOR

Medtronic

AN EXTENSION **OF YOU**

Telescope™ Guide Extension Catheter

The performance you want for your complex clinical practice:

- **Superior deliverability[1]**
- **Softest[2] tip — TruFlex™ soft polymer tip**
- **SmoothPass Technology — helps you channel PCI devices**

Lengths ahead in diabetic patient outcomes

UNIQUE

BETTER

LONGER

UNIQUE | BETTER | LONGER

Polymer-free

- Abluminal Reservoir Technology
- Amphilimus™ formulation Sirolimus + Organic Acid
- Bio-Inducer Surface coating

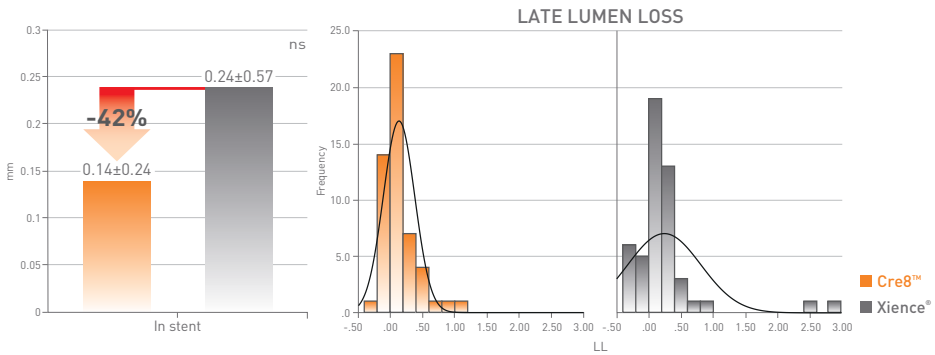
The RESERVOIR clinical trial: independent randomized comparison of Cre8™ vs Xience® in patients with Diabetes Mellitus*

PI Dr. R. Romaguera

Randomization 1:1

Cre8™ 56 pts — Xience® 56 pts

ANGIOGRAPHIC RESULTS AT 6 MONTHS



CRE8™ HIGHLY REDUCES LLL WITH A BETTER RESULT CONSISTENCY

Ø (mm)	length 46 mm
2,50	*
2,75	*
3,00	*
3,50	*

Funded by the Spanish Society of Cardiology

*Romaguera et al. JACC: CARDIOVASCULAR INTERVENTIONS VOL.9,NO.1,2016:42–50

DIABETIC PATIENTS

Cre8™

AMPHILIMUS™ ELUTING CORONARY STENT

Alvimedica

Manufactured by **CID** S.p.A. member of Alvimedica Group
Strada per Crescentino, sn - 13040 Saluggia (VC), Italy

www.alvimedica.com

Currently not available in US and Japan.

Please consult product labels and package inserts for indications, contraindications, hazards, warnings, cautions and instruction for use.