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

Severe In-Stent Restenosis due to Two Stent Layers: A Case Report
Tesna In-Stent Restenoza uzrokovana postojanjem dva sloja stenta: Prikaz slučaja

Treatment of cardiogenic shock in PCI center without the possibility of mechanical circulatory support - case report and review of the contemporary data
Perkutana koronarna intervencija kod pacijenta sa kardiogenim šokom u centru bez mogućnosti mehaničke cirkulatorne potpore: Prikaz slučaja i pregled postojeće literature

In-stent restenosis: neointimal priliferation or neoatherosclerosis
In-stent restenoza: neointimalna proliferacija ili neoateroskleroza

Recurrent Percutaneous Coronary Interventions in a Patient With a Single Coronary Ostium Arising From the Right Coronary Sinus: An 18-Year Clinical Course
Ponovljena perkutana koronarna intervencija kod pacijenta sa jedinim koronarnim otstupom iz desnog koronarnog sinusa: 18-godišnji klinički tok

Transcatheter Aortic Valve Implantation in Large and Extra-Large Aortic Annuli: Contemporary Evidence and Performance of Third-Generation Devices
Transkateterska zamena aortnog zaliska kod pacijenata sa velikim i veoma velikim aortnim anulusom: Savremeni dokazi i performanse zalistaka treće generacije

Volumen 44 Broj 4
2025. godina

U ovom broju se nalaze radovi koji će biti prezentovani na 11. ZASINK 2025 kongresu

PHARMASWISS

BelKombo

ramipril/bisoprolol

KADA SRCE TRAŽI BIS

Dva leka koja se najčešće koriste za lečenje kardiovaskularnih bolesti - u jednoj kapsuli[1]

SAMO ZA STRUČNU JAVNOST
Lek se izdaje uz lekarski recept.
Detaljne informacije o leku možete naći u Sažetku karakteristika leka:
BELKOMBO®, 2,5mg/1,25mg, datum poslednje revizije februar 2024.
BELKOMBO®, 2,5mg/2,5 mg, 5mg/2,5mg, 5mg/5mg, 10mg/5mg, datum poslednje revizije februar 2024.
Reference:
1. Iqvia Sell out data, MAT Jun 2024, preuzeto 9.7.2024.

Broj i datum izdavanja dozvole za stavljanje leka u promet:
BELKOMBO®, kapsule, tvrde 30 x (2,5 mg/1,25 mg): 000461944 2023 od 26.02.2024.
BELKOMBO®, kapsule, tvrde, 30 x (2,5 mg/2,5 mg): 000461945 2023 od 26.02.2024.
BELKOMBO®, kapsule, tvrde, 30 x (5 mg/2,5 mg): 000461946 2023 od 26.02.2024.
BELKOMBO®, kapsule, tvrde, 30 x (5 mg/5 mg): 000461280 2023 od 26.02.2024.
BELKOMBO®, kapsule, tvrde, 30 x (10 mg/5 mg): 000461281 2023 od 26.02.2024.

Nosilac dozvole za stavljanje leka u promet:
PHARMASWISS D.O.O., Batajnički drum 5 A, Beograd
ALIMS broj rešenja:
002558436 2024 59010 006 000 515 069 04 002 od 21.10.2024.
002558442 2024 59010 006 000 515 069 04 002 od 5.12.2024.
RAMIPRIL-RS-24-8-363-M

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 44 Broj 4 2025. 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: markobanovic71@gmail.com, naslovljeno na: Marko Banović, 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:
Marko Banović
Editor-in-Chief, Heart and Blood Vessels
and mailed to markobanovic71@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 44, Broj 4
Beograd, Višegradska 26: Udruženje kardiologa Srbije
2025 Beograd: Newassist doo
Tromesečno-Broj 1 izašao 2011. god.

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

UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA

SRCE I KRVNI SUDOVI
HEART AND BLOOD VESSELS

Volumen 44 Broj 4 2025. godina

Sadržaj / *Content*

Srce i krvni sudovi 2025; 44(4): 111-115

Case report

Severe In-Stent Restenosis due to Two Stent Layers: A Case Report

Pavel Somov[1], Dmitriy Marchak[1], Arkhip Matusov[1]

[1]*Pirogov's National Medical Surgical Center, Moscow, Russian Federation*

Abstract

Background: The prevalence of in-stent restenosis is around 3-10%. One treatment option for restenosis is implantation of another drug eluting stent, the so-called "sandwich strategy". Multiple stent layers can potentially reduce the penetration of antiproliferative drugs into the vessel wall, thereby minimizing the effect of the drug. In this clinical case, we encountered restenosis after a previously implanted stent for treatment of restenosis.

Case presentation: A 73-year-old female with previous history of RCA stenting in 2019 due to myocardial infarction. In 2020, RCA restenosis was identified and RCA PCI was performed (Supraflex 2.75x28mm, XienceXpedition 3.5x38mm). The current hospitalization was associated with a recurrence of dyspnea on exertion. Coronary angiographyrevealedan 80% restenosis of the RCA. A decision was made to perform ultra-high-pressure balloonfor this lesion. A stent-boost image was obtained showing stent deformation. Balloon angioplasty was performed using a 3.5x15mm ultra-high-pressure balloon OPN NC (SIS Medical, Switzerland) at 40 atm. Control angiography showed a restoration of vessel lumen. IVUS showed minimal lumen area (MLA) of 8.37 mm^2. Six months latercause of a recurrence of dyspnea on exertion a myocardial scintigraphy was performed, which revealed an ischemic zone of 20-25%. Based on these results, angiography was performed which identified recurrent restenosis in the same segment. IVUS-guided angioplasty with a 4.0x15mm OPN NC in combination with a 4.0x30mm Agent drug-coated balloon (DCB) was performed with inflation at 6 atm for 60 seconds. This resulted in good angiographic results, with an MLA of 9.76mm²and optimal stent expansion throughout.

Conclusion: Treatment of patients with restenosis remains a challenging task. Intravascular imaging is a fundamental factor in restenosis management, allowing determination of restenosis type and selection of optimal treatment strategy to achieve satisfactory results and reduce the risk of repeat interventions.Therefore, the combination of intravascular imaging and dedicated devices is strongly suggested for a more standardized approach for in-stent restenosis.

Key-words In-stent restenosis, Multiple stent layers, Intravascular image

Introduction

Despite the use of 2nd and 3rd generation drug-eluting stents (DES), the risk of developing in-stent restenosis (ISR) remains at 3-10%[1]. One treatment option for restenosis is implantation of another drug eluting stent, the so-called "sandwich strategy[2]. However, a large amount of neointimal hyperplasia and multiple stent layers can potentially reduce the penetration of antiproliferative drugs into the vessel wall, thereby minimizing the effect of the drug[3-5]. In this clinical case, we encountered an ISR after a previously implanted stent for treatment of an ISR.

Clinical Case

A 73-year-old female patient was admitted to our center. From the medical history, it was known that in 2017 coronary artery bypass grafting was recommended due to three-vessel coronary disease, which the patient refused. In 2019, myocardial infarction and percutaneous coronary intervention (PCI) of the right coronary artery (RCA) and left anterior descending artery (LAD) were performed. In 2020, RCA ISR was identified and PCI was performed on the RCA (Supraflex 2.75x28mm, XienceXpedition 3.5x38mm). The current hospitalization was associated with a recurrence of complaints of dyspnea on exertion. Coronary angiography was performed, revealing 80% ISR of the RCA (Figure 1). A decision was made to perform ultra-high-pressure balloonangioplasty for this lesion. Using a right radial approach with a 6F JR4 Launcher (Medtronic, USA),aRinato guidewire (AsahiIntecc, Japan) was advanced into the distal vessel. Intravascular ultrasound (IVUS) examination was performed (Opticross 40, Boston Scientific, USA) (Figure 2). Minimum lumen area was 3.26 mm². A stent-boost image was obtained (Figure 3) showing stent deformation. Balloon angioplasty was performed using 3.0x15mm NC Sprinter (Medtronic, USA), and a 3.5x15mm ultra-high-pressure balloon OPN NC(SIS Medical, Switerland) at 40 atm. Figure 4 shows balloon expansion in stent-boost mode. Figure 5 demon-

Corresponding author: Dr Pavel Somov, Doc.p.somov@gmail.com

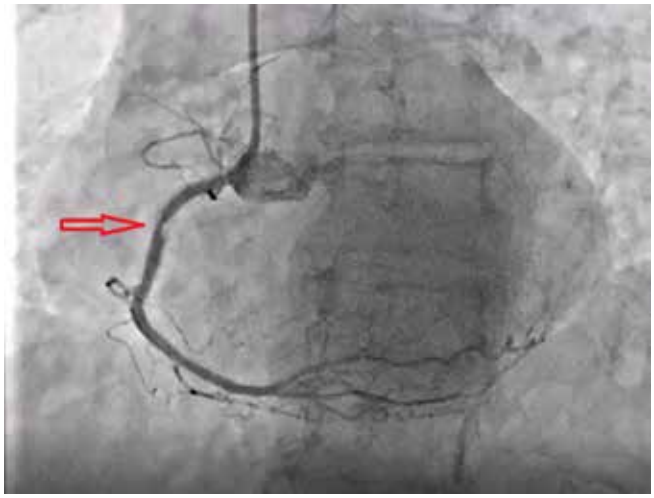


Figure 1. RCA restenosis

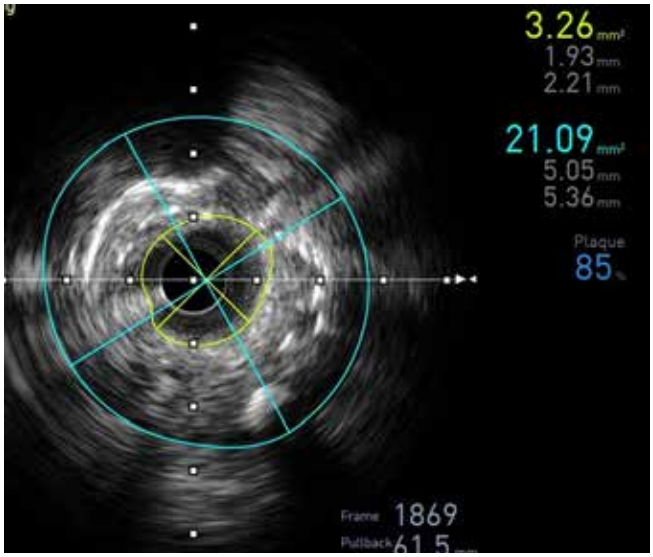


Figure 2. IVUS of RCA restenosis

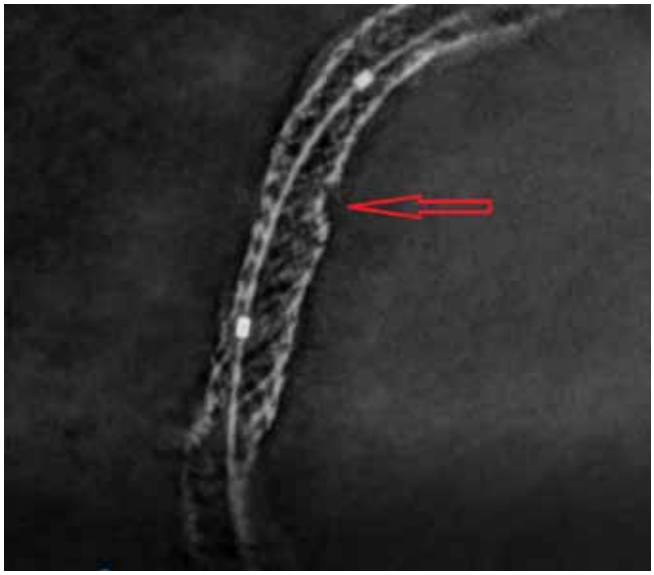


Figure 3. Stent deformation (stent-boost)

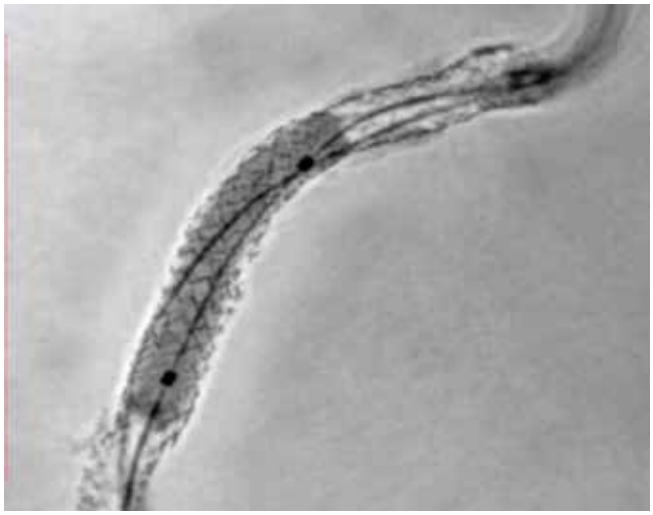


Figure 4. Balloon expansion (stent-boost)

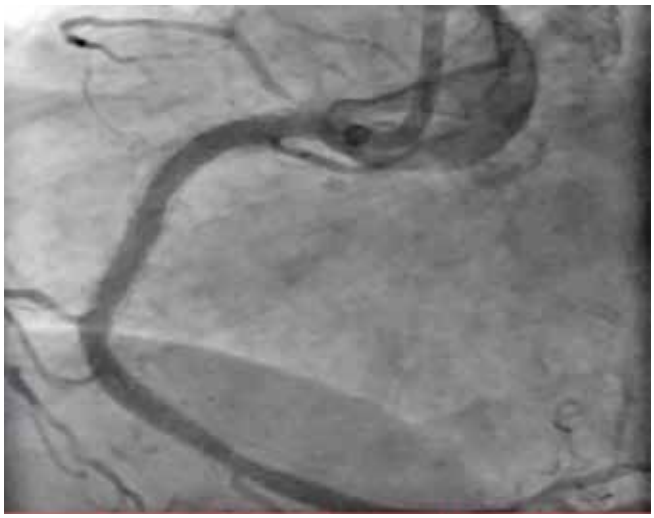


Figure 5. Angio result

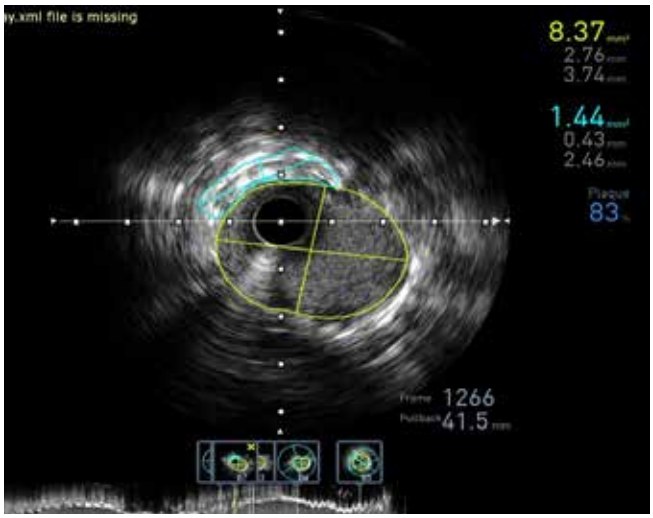


Figure 6. IVUS control. Minimum lumen area 8.37 mm²

strates control angiography with restoration of vessel lumen. IVUS showed minimum lumen area of 8.37 mm² (Figure 6), with neocalcification area and structures of the two previously implanted stents highlighted in blue. The patient was prescribed atorvastatin 40mg, clopidogrel 75mg, aspirin 100mg, and ezetimibe 10mg. Six months later, cause of a recurrence of dyspnea on exertion a myocardial scintigraphy was performed, which revealed an ischemic zone of 20-25% (Figure 7). Based on these results, angiography was performed which identified recur-

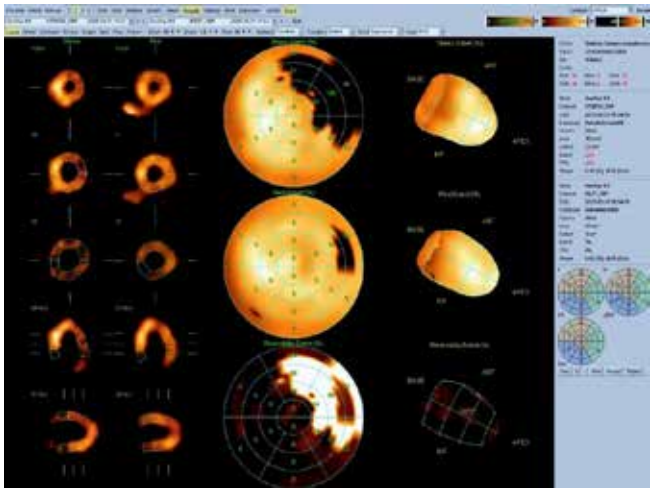


Figure 7. Myocardial scintigraphy

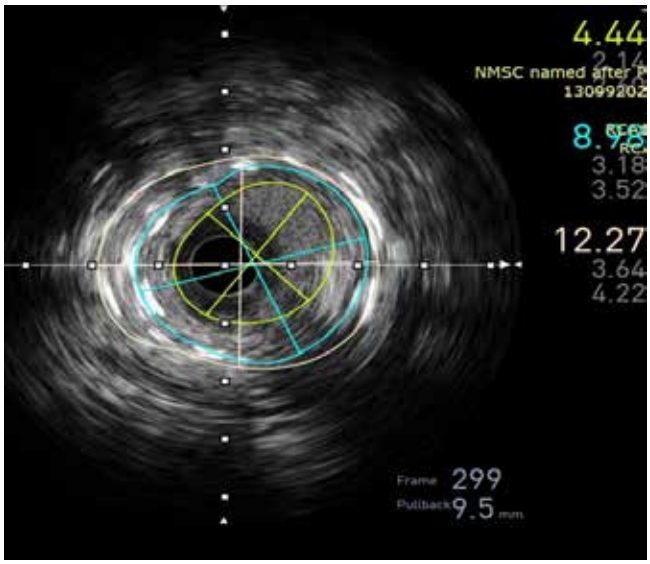


Figure 9. IVUS of restenosis

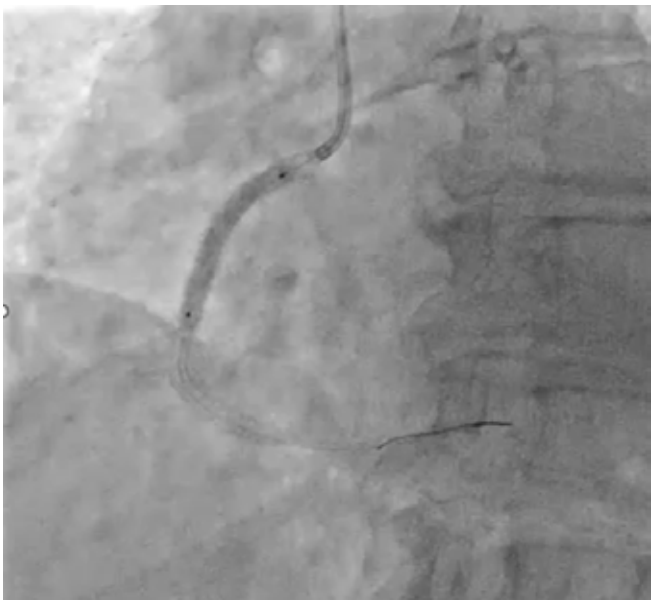


Figure 11. DCB 4.0x30

rent ISR in the same segment (Figure 8). After the discussion of the case with our Heart Team we decided to perform drug-coated balloon (DCB) angioplasty. IVUS was performed (Figure 9) and repeat angioplasty with an ultra-high-pressure balloon in combination with a drug-

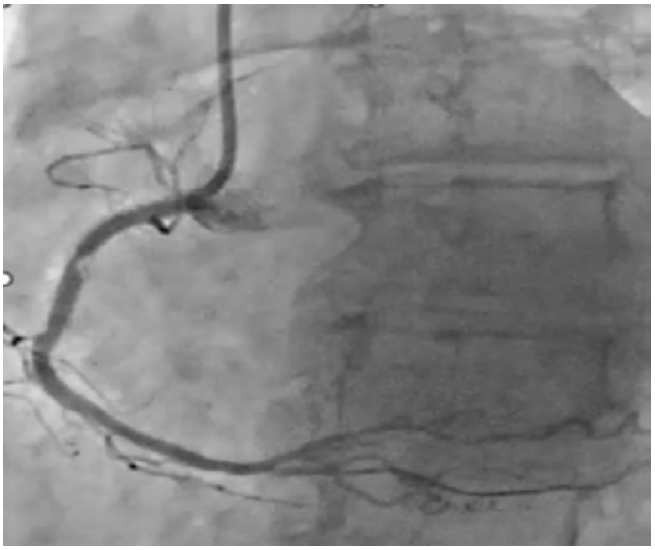


Figure 8. Recurrent RCA restenosis

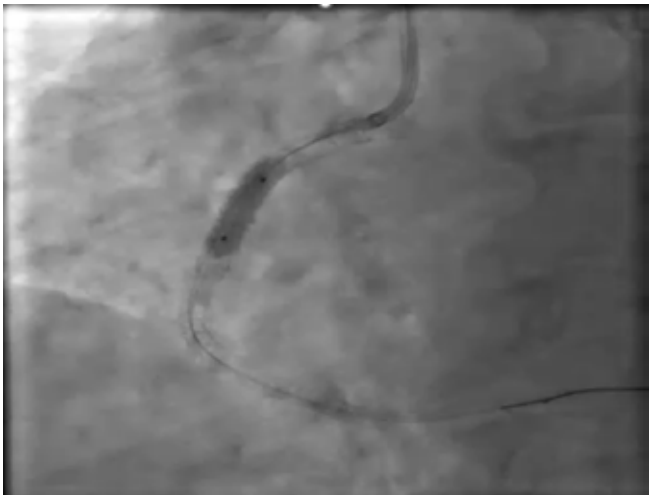


Figure 10. OPN 4.0x15

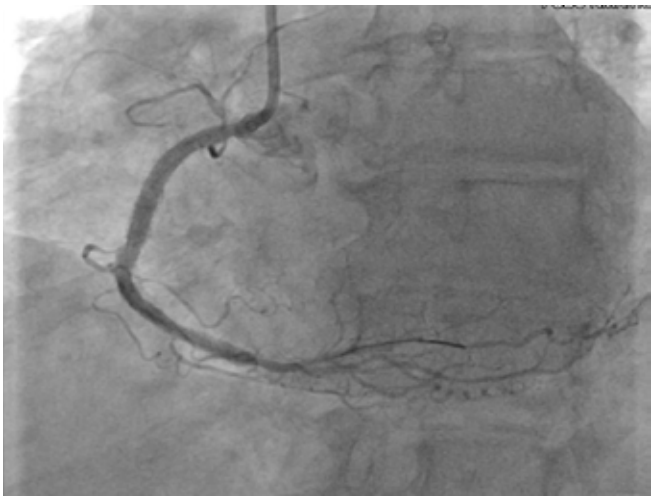


Figure 12. Angio result

coated balloon was planned. Balloon angioplasty with 4.0x15mm OPN NC (SIS Medical, Switzerland)(Figure 10) was done. DCB angioplasty with 4.0x30mm Agent (Boston Scientific, USA) (Figure 11) was performed with inflation for 60 seconds at 6 atm. This resulted in good angiographic result (Figure 12), and MLA on IVUS of 9.76 mm² (Figure 13) with optimal stent expansion throughout.At the six-month follow-up, the patient remained angina free.

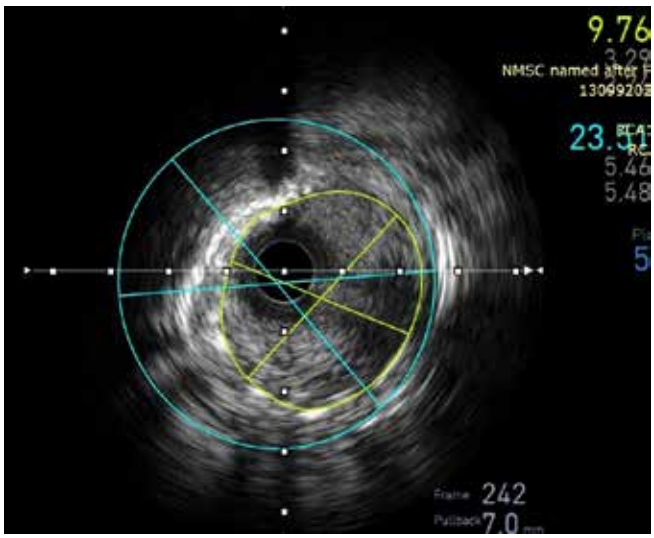


Figure 13. IVUS control

Discussion and Conclusion

There are various strategies for treating DES ISR. Repeated DES implantation compared with DCB application has shown the most favorable results regarding repeat restenosis. However, repeated stent implantation leads to reduction in vessel lumen and increases the risk of stent thrombosis[6-8]. The ISAR-DESIRE 3 study showed comparable results of using DCB and DES in treating restenosis[9]. Upon examination of angiograms with stent-boost mode, we identified stent deformation, therefore we encountered not only restenosis after implantation of two stent layers, but also deformation of the previously stented segment, which further complicated the correction of this lesion. According to the Waksman classification, in this case there is combined restenosis Type 1 (mechanical stent deformation) and Type 5 (2 or more stent layers)[10]. In complex restenosis cases, the use of ultra-high-pressure balloons OPN NC (SIS Medical, Switzerland) is the correct choice for two reasons: first, to achieve greater vessel lumen through re-expansion of previously placed stents. Second, to increase lumen by compression of neointimal tissue that appears during restenosis, which is confirmed using IVUS[11]. In our clinical case, intravascular imaging, ultra-high-pressure balloons, and DCB were used for treatment of complex ISR. According to the restenosis treatment algorithm (Figure 14) proposed by Shlofmitz et al., we selected the optimal treatment strategy for this lesion[12]. However, in the first intervention, a DCB was not used, which likely led to recurrent restenosis at 6 months. During repeat treatment of restenosis, larger ultra-high-pressure balloons were used based on IVUS results (Figure 9), and 4.0x30mm Agent DCB (Boston Scientific, USA) was utilized.At the six-month follow-up, she remained angina free. The current guidelines on myocardial revascularization recommend re-stenting with DES and the use of DCB. In our case, the overlap of multiple stent layers was known, so re-stenting with DES might raise concerns about the addition of metallic layer. The multiple layers may cause further endothelial growth associated with stent thrombosis and recurrent ISR. An OPN balloon was used to expand deformed segment and DCB was used to avoid the additional metallic layer

Treatment of patients with restenosis remains a challenging task. Intravascular imaging is a fundamental factor in restenosis management, allowing determination of restenosis type and selection of optimal treatment strategy to achieve satisfactory results and reduce the risk of repeat interventions.Therefore, the combination of intravascular imaging and dedicated devices is strongly suggested for a more standardized approach for treatment of ISR.

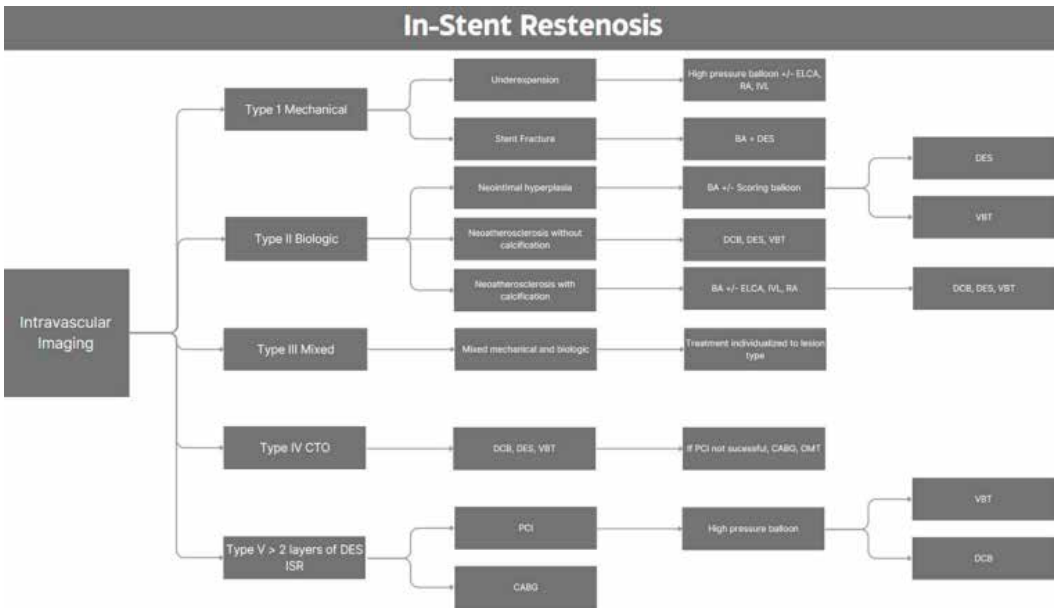


Figure 14. Algorithm of ISR treatment.

BA indicates balloon angioplasty; CABG, coronary artery bypass graft; CTO, chronic total occlusion; DCB, drug-coated balloon; DES, drug-eluting stent; ELCA: excimer laser coronary atherectomy; ISR, in-stent restenosis; IVL, intravascular lithotripsy; IVUS, intravascular ultrasound; OCT, optical coherence tomography; OMT, optimal medical therapy; PCI, percutaneous coronary intervention; RA, rotational atherectomy; and VBT, vascular brachytherapy.

References

1. Moussa ID, Mohananey D, Saucedo J, et al. Trends and Outcomes of Restenosis After Coronary Stent Implantation in the United States. J Am Coll Cardiol. 2020 Sep 29;76(13):1521-1531. doi: 10.1016/j.jacc.2020.08.002. PMID: 32972528.
2. Alfonso F, Scheller B. Management of recurrent in-stent restenosis: onion skin full metal jacket? EuroIntervention. 2013;9: 781-5.
3. Maluenda G, Ben-Dor I, Gaglia MA Jr, et al. Clinical outcomes and treatment after drug-eluting stent failure: The absence of traditional risk factors for in-stent restenosis. Circ Cardiovasc Interv 2012; 5(1): 12-9. http://dx.doi.org/10.1161/CIRCINTERVENTIONS.111.963215 PMID: 22319069
4. Mintz GS. Features and parameters of drug-eluting stent deployment discoverable by intravascular ultrasound. Am J Cardiol. 2007;100:26M-35M.
5. Pleva L, Kukla P, Hlinomaz O. Treatment of coronary in-stent restenosis: a systematic review. J Geriatr Cardiol JGC. 2018;15:173-184. doi: 10.11909/j.issn.1671-5411.2018.02.007
6. Giacoppo D, Alfonso F, Xu B, et al. Paclitaxel-coated balloon angioplasty vs. drug-eluting stenting for the treatment of coronary in-stent restenosis: a comprehensive, collaborative, individual patient data meta-analysis of 10 randomized clinical trials (DAEDALUS study). Eur Heart J. 2020;41(38):3715-3728. https://doi.org/10.1093/eurheartj/ehz5947
7. Kawamoto H, Ruparelia N, Latib A, et al. Drug-coated balloons versus second-generation drug-eluting stents for the management of recurrent multimetal-layered in-stent restenosis. J Am Coll CardiolIntv. 2015;8(12):1586-1594. https://doi.org/10.1016/j.jcin.2015.04.032
8. Alfonso F, Garcia J, Perez-Vizcayno MJ, et al. New stent implantation for recurrences after stenting for in-stent restenosis: implications of a third metal layer in human coronary arteries. J Am Coll Cardiol. 2009;54(11):1036-1038. https://doi.org/10.1016/j.jacc.2009.04.082
9. Giacoppo D, Alvarez-Covarrubias HA, Koch T, et al. Coronary artery restenosis treatment with plain balloon, drug-coated balloon, or drug-eluting stent: 10-year outcomes of the ISAR-DESIRE 3 trial. Eur Heart J. 2023 Apr 17;44(15):1343-1357. doi: 10.1093/eurheartj/ehad026. PMID: 36807512.
10. Waksman R, Iantorno M. Refractory In-Stent Restenosis: Improving Outcomes by Standardizing Our Approach. Curr Cardiol Rep. 2018 Oct 22;20(12):140. doi: 10.1007/s11886-018-1076-6. PMID: 30350271.
11. Shah M, Najam O, Bhindi R, et al. Calcium Modification Techniques in Complex Percutaneous Coronary Intervention. Circ Cardiovasc Interv. 2021 May;14(5):e009870. doi: 10.1161/CIRCINTERVENTIONS.120.009870. Epub 2021 Jan 14. PMID: 33441017.
12. Shlofmitz, E, Iantorno, M, Waksman, R. Restenosis of Drug-Eluting Stents: A New Classification System Based on Disease Mechanism to Guide Treatment and State-of-the-Art Review. Circ. Cardiovasc. Interv. 2019, 12, e007023.

Sažetak

Tesna In-Stent Restenoza uzrokovana postojanjem dva sloja stenta: Prikaz slučaja

Pavel Somov[1], Dmitriy Marchak[1], Arkhip Matusov[1]

[1]Pirogov's Nacionalni Centar za Hirurgiju, Moskva, Ruska Federacija

Uvod: *Prevalenca restenoze u stentu je oko 3-10%. Jedna od opcija lečenja restenoze je implantacija još jednog stenta koji oslobađa lek, takozvana „sendvič strategija". Višestruki slojevi stenta mogu potencijalno smanjiti prodor antiproliferativnih lekova u zid krvnog suda, čime se minimizira efekat leka. U ovom kliničkom slučaju, naišli smo na restenozu nakon prethodno implantiranog stenta za lečenje restenoze.*

Prikaz slučaja: *73-godišnja žena sa prethodnom istorijom stentiranja desne koronarne arterije (DKA) 2019. godine zbog infarkta miokarda. 2020. godine identifikovana je restenoza DKA i izvršena je ponovna perkutana koronarna intervencija (PKI) DKA (Supraflex 2,75x28 mm, XienceXpedition 3,5x38 mm). Aktuelna hospitalizacija je bila povezana sa ponovnom pojavom dispneje pri naporu. Koronarna angiografija je otkrila 80% restenoze DKA. Doneta je odluka da se za ovu leziju izvede stentiranje balonom ultravisokog pritiska. Dobijena je slika stent-busta koja prikazuje deformaciju stenta. Balonska angioplastika je izvršena pomoću balona ultravisokog pritiska 3,5x15 mm OPN NC (SIS Medical, Švajcarska) na 40 atm. Kontrolna angiografija je pokazala restauraciju lumena krvnog suda. Intravenozni ultrazvuk (IVUS) je pokazao minimalnu površinu lumena (MLA) od 8,37 mm2. Šest meseci kasnije, zbog ponovne dispneje pri naporu, urađena je scintigrafija miokarda, koja je otkrila ishemijsku zonu od 20-25%. Na osnovu ovih rezultata, urađena je ponovna angiografija koja je identifikovala rekurentnu restenozu u istom segmentu. Intravaskularnim ultrazvukom vođena angioplastika sa balonom 4,0x15 mm OPN NC u kombinaciji sa 4,0x30 mm balonom obloženim lekom (DCB) izvršena je sa inflacijom na 6 atm tokom 60 sekundi. Ovo je rezultiralo dobrim angiografskim rezultatima, sa MLA od 9,76 mm² i optimalnim širenjem stenta.*

Zaključak: *Lečenje pacijenata sa restenozom stenta je i dalje izazovno. Intravaskularn imidžing je fundamentalni faktor u uspešnom lečenju restenoze, omogućavajući određivanje tipa restenoze i izbor optimalne strategije lečenja kako bi se postigli zadovoljavajući rezultati i smanjio rizik od ponovljenih intervencija. Stoga se snažno preporučuje kombinacija intravaskularnog imidžinga i posvećenih uređaja za standardizovani pristup lečenja restenoze u stentu.*

Ključne reči: *Restenoza, Slojevi stenta, Intravskularni imidžing*

Srce i krvni sudovi 2025; 44(3) : 116-121

Case report

Treatment of cardiogenic shock in PCI center without the possibility of mechanical circulatory support - case report and review of the contemporary data

Nikolić Milan[1], Mitov Vladimir[1], Jolić Aleksandar[1], Adamović Dragana[1], Nikolić Milena[2]

[1]Department of invasive cardiology, Health center Zaječar, [2] Department of anaestesiology and reanimatology, Health center Zaječar

Abstract

Introduction: Cardiogenic shock (CS) is one of the most severe conditions met in the cardiac intensive care unit, with a short-term mortality rate of 30–40%. It represents a syndrome of hypoperfusion and organ dysfunction due to a primarily cardiac cause, most commonly as a consequence of acute myocardial infarction (AMI).

Aim: To present a case of an advanced age female patient treated for CS following acute myocardial infarction in a PCI center without the availability of mechanical circulatory support.

Case report: An 85-year-old female patient was admitted to the Invasive cardiology department of Health Center Zaječar, presenting with an anterior wall STEMI, 9 hours after the onset of chest pain in Forrester class III CS. Primary PCI of the LAD was performed, after which she was treated with inotropic support of norepinephrine in a maximal dose of 0.35 mcg/kg/min, along with cautious infusion of crystalloid fluids and other heart failure therapy. Upon the administered therapy, the patient hemodynamically stabilized and inotropic stimulation ceased despite ongoing severe left ventricular systolic dysfunction with an EF of 15–20% and severe mitral regurgitation. The further clinical course was complicated by aspiration pneumonia, diarrheal syndrome, and dehydration with hypernatremia, eventually resulting in a fatal outcome after 21 days of treatment.

Conclusion: Emergency primary PCI procedure in the nearest PCI center, along with the administration of inotropic agents and other supportive measures in the cardiac intensive care unit, can lead to hemodynamic stabilization even in critically ill patients of advanced age with CS.

Key-words acute myocardial infarction, STEMI, cardiogenic shock, inotropic agents, norepinephrine

Introduction

Cardiogenic shock (CS) represents a syndrome of hypoperfusion and organ dysfunction due to a primarily cardiac cause, with a decreased cardiac output[1]. The clinical definition implies a systolic pressure below 90 mmHg lasting longer than 30 minutes, or maintained above these values by the administration of inotropes/vasopressors; and signs of tissue hypoperfusion: oliguria (diuresis less than 30 ml/h), altered mental status, skin pallor and coldness. Laboratory markers of tissue hypoperfusion are elevated levels of serum lactate above 2 mmol/L; alanine transaminaase (ALT) above 200 or more than 3 times the upper reference limit; serum creatinine more than 2 times the upper reference limit; arterial blood pH less than 7.2, without other causes of acidosis. CS is one of the most common causes of admission to the cardiac intensive care unit (coronary care unit), with a short-term mortality rate of 30–40% and a one-year mortality rate of around or over 50%[2].

Here we present a case of an elderly female patient with CS caused by acute myocardial infarction (AMI), treated with primary percutaneous coronary intervention (pPCI) and inotropic agents in a secondary-level healthcare facility, without the possibility of mechanical circulatory support.

Case report

An 85-year-old female patient was admitted to the Department of invasive cardiology of the Zaječar Health Center nine hours after the onset of continuous chest pain. Electrocardiography revealed ST-segment elevation in precordial leads (Figure 1). Upon admission, the patient was hemodynamically unstable with BP 70/40 mmHg, HR 110/min, pale, cold skin, and without signs of pulmonary congestion, corresponding to CS (Killip IV, Forrester III class). Emergency coronary angiography was performed, revealing lesions in the ostial segment of the Cx and a longer atherosclerotically narrowed segment of OM2, as well as an ostially occluded LAD (Figures 2 and 3). Standard coronary guidewires (BMW, Asahi SIon Blue) could not cross the lesion, so a Pilot 50 coronary wire was used, followed by predilatations with Sapphire 1x10 and Sprinter Legend 2x20 balloons. Two lesions were identified—one in the ostial part of LAD and the

Corresponding author: Vladimi Mitov, MD, PhD, drvladimirmitov@gmail.com

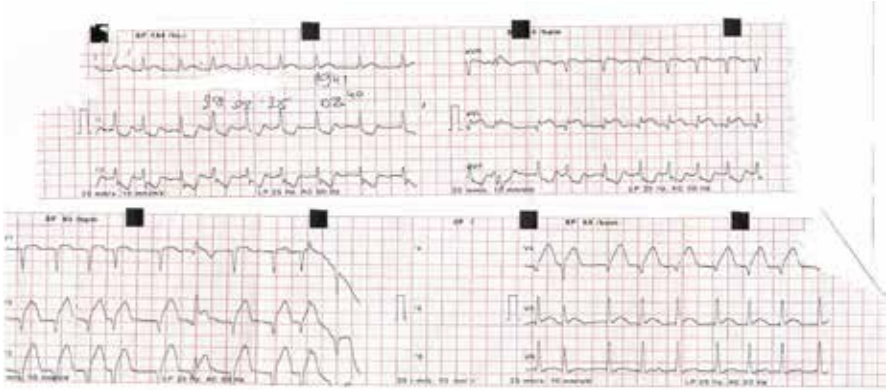


Figure 1.

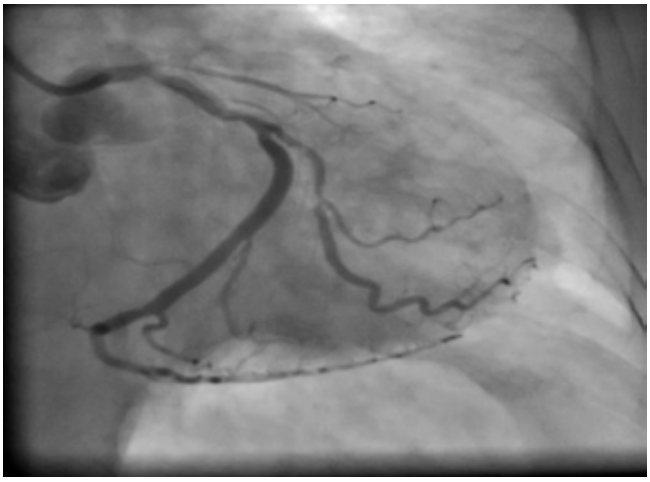


Figure 2.

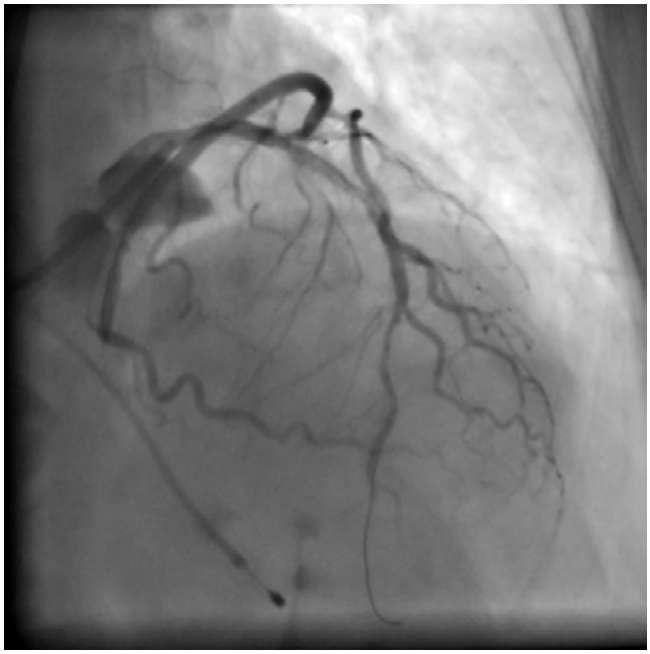


Figure 4.

other in the medial segment of LAD. A Synsiro PRO 2.75x26 stent was implanted in the medial stenosis, after which a *no-reflow* phenomenon occurred. Through a microcatheter, 500 mcg of Verapamil was applied into the distal segment of the artery, resulting in a TIMI 2–3 flow through the LAD with a residual LM–LAD stenosis of 50–60% (Figure 4). A temporary pacemaker electrode was placed, with a pacing rate of 100/min.

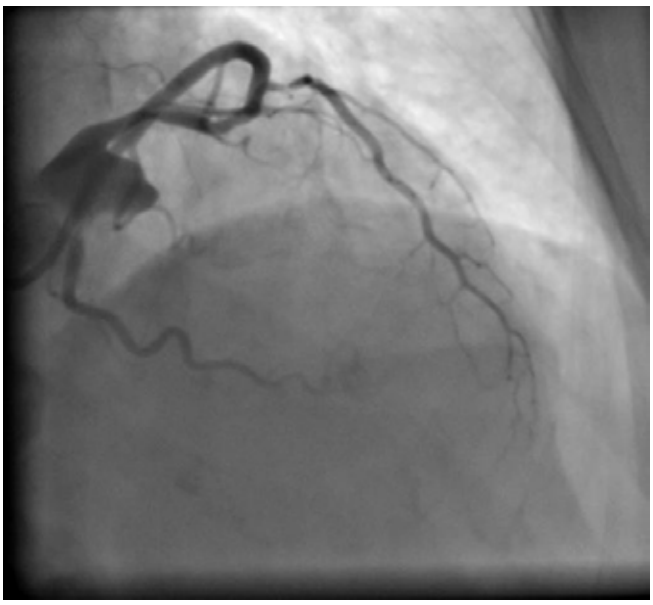


Figure 3.

During the procedure, the patient remained hemodynamically unstable, on oxygen therapy, with a brief respiratory arrest followed by spontaneous breathing. After the procedure, she was transferred to the Coronary Care Unit, and inotropic support with norepinephrine was initiated through the right femoral vein at an initial dose of 0.2 mcg/kg/min, titrated according to therapeutic response over 48 hours up to a maximum of 0.35 mcg/kg/min. From the second hospital day, as there were no signs of pulmonary congestion, a "fluid challenge" with 1 L of crystalloids per day was administered, without the development of dyspnea or pulmonary congestion. Hemodynamic improvement was achieved, and after 48 hours inotropes and oxygen therapy were discontinued, and the temporary pacemaker electrode was removed, with a daily diuresis of 1000 ml.

The subsequent hospital course was complicated by right-sided pneumonia, treated empirically with cefepime and levofloxacin, followed by diarrheal syndrome with hypertonic dehydration and severe hypernatremia (up to 164 mmol/L). Throughout the hospital course, the patient remained hemodynamically stable with "dry" lungs. Echocardiography performed on the fifth hospital day indicated severely impaired global left ventricular function with an estimated left ventricular ejection fraction (LVEF) of 15–20% and akinesia of the anterior sep-

tum, apical and medial segment of the inferior septum, as well as the entire anterior and lateral wall. The right heart chambers were dilated, with TR 3–4+ and estimated pulmonary artery systolic pressure of about 50 mmHg. After 21 days of treatment, despite all therapeutic measures applied and the patient's hemodynamic stability, the patient died.

Discussion

CS may arise from multiple etiologies, among which AMI has traditionally been the most frequent cause. Less common etiologies include various forms of *de novo* cardiac dysfunction such as right ventricular failure, Takotsubo syndrome, peripartum cardiomyopathy, fulminant myocarditis, valvular heart disease, or decompensation of chronic heart failure[3]. Although historically about 80% of cardiogenic shock cases were attributed to acute myocardial infarction[4], more recent registry data suggest that the epidemiology has shifted in recent decades, with decompensated heart failure now representing an increasingly prevalent cause[5–7].Given that the case report involves AMI-related CS, the following discussion focuses on this clinical subtype.

Before the advent of pharmacologic and mechanical reperfusion strategies, CS frequently complicated AMI. In the landmark study by Killip *et al*[8], published in 1967, 250 patients had a definite diagnosis of myocardial infarction in a single hospital in a two-year period, with CS occurring in 19% of cases. In the early 2000s, the incidence of CS was reported in approximately 8% of STEMI and 5% of NSTEMI patients[9].

Despite major advances in myocardial revascularization and the development of short-term mechanical circulatory support over the past two decades, randomized clinical trials have largely failed to identify additional therapeutic interventions that significantly reduce mortality from AMI-related cardiogenic shock beyond revascularization itself[10]. Notably, the SHOCK registry found no statistically significant difference in 30-day mortality between patients who underwent urgent myocardial revascularization (PCI or surgical) and those initially managed with medical stabilization including systemic fibrinolysis. However, at 6- and 12-month follow-up, patients who underwent early mechanical revascularization demonstrated substantially lower mortality (50.3% and 53.3% vs. 63.1% and 66.4%, respectively)[11]. The registry also described the temporal profile of shock onset. On average, CS developed 6.2 hours after the onset of chest pain: 1.7 hours when the culprit lesion was in the left main coronary artery, 3.5 hours in the right coronary artery, 3.9 hours in the circumflex artery, 11 hours in the LAD, and 10.9 hours in a saphenous vein graft. Early shock (within 24 hours of symptom onset) was associated with chest pain as the presenting symptom, ST-segment elevation in two or more ECG leads, smoking, multivessel disease, and left main artery disease. Late shock (more than 24 hours after symptom onset) was more often linked to recurrent ischemia, development of Q waves in two or more leads, and anterior infarction. Mortality was higher in early compared with late shock (62.6% vs. 53.6%)[12].

Yang *et al*[13] proposed the EARLY SHOCK scoring system, identifying eight prehospital variables independently predicting high risk of developing CS: heart rate, systolic blood pressure at presentation, diabetes, dialysis status, age, prehospital cardiac arrest, and infarct localization. The strongest predictors were systolic blood pressure at presentation below 90 mmHg (OR 17.76) and prehospital cardiac arrest (OR 18.32), while anterior infarction carried a moderately increased risk compared with non-anterior localization (OR 1.58).

Our patient presented nine hours after symptom onset with an ostial LAD occlusion, and the prolonged duration of ischemia involving a large myocardial territory resulting in the development of CS upon presentation. The time interval between symptom onset and first medical contact (FMC) remains prolonged in various parts of the world. Data from the GRACE registry indicate that this interval averages around two hours in the United States and Canada[14]. In a cohort study from Ontario, Canada, as many as 66% of patients had a symptom-onset-to-FMC time exceeding 120 minutes[15]. Unfortunately, this trend has persisted over the past two decades despite public awareness campaigns and other interventions. Delayed presentation is more common among women and elderly patients[16–18]. Local data from Eastern Serbia show a similar pattern: in 2019, the average time to FMC was 222 minutes, and in 2020, due to the COVID-19 pandemic and fear of seeking medical care, increased to 302 minutes[19].

Our patient's clinical presentation corresponded to Forrester class III cardiogenic shock ("dry and cold")[20]. She showed no clinical signs of pulmonary congestion and was therefore able to undergo primary PCI in the supine position with supplemental oxygen therapy, without the need for mechanical ventilation. In their seminal study, Forrester *et al* performed right heart catheterization in patients with AMI-related-CSI and, using hemodynamic parameters (cardiac index and pulmonary capillary wedge pressure), defined four clinical subsets. The first two classes were characterized by the absence of hypoperfusion (cardiac index > 2.2 L/min/m²), whereas classes III and IV demonstrated a reduced cardiac index, with normal (class III) or elevated (class IV) pulmonary wedge pressure. Mortality increased progressively with higher class—from 2.2% in class I to 55.5% in class IV. Class III, into which our patient was stratified, carries an estimated mortality rate of 22.4%. As right heart catheterization was not feasible in our facility, classification was based on clinical parameters. Notably, the accuracy of clinical assessment in predicting hemodynamic abnormalities was found to be satisfactory—approximately 83%—in a subsequent analysis by Forrester *et al*.[21].

An important question arises regarding the appropriateness of fluid challenge in patients with Forrester class III CS. Most clinicians in everyday practice tend to avoid fluid administration due to the fear of inducing pulmonary edema, even when the pulmonary capillary wedge pressure (PCWP) is not elevated. In the present case, after initial stabilization, the patient received 1LL of crystalloid solutions daily without the development of pulmonary congestion. Early studies involving right heart catheterization demonstrated that intravascular volume

expansion may improve cardiac index. It has been shown that a 50% increase in PCWP can lead to a 19% increase in cardiac index, without affecting systolic arterial pressure. Thus, an improvement in cardiac index through crystalloid infusion can be achieved while maintaining PCWP below the pulmonary congestion treshold[22].

Following hospital admission and the diagnosis of anterior wall STEMI in our patient, coronary angiography and primary PCI were performed. Due to hemodynamic instability, only the left coronary system was cannulated. In addition to the culprit lesion involving the left main and LAD, a significant angiographic lesion was observed in the OM2 branch. Only the LAD lesions were treated, in accordance with the findings of the CULPRIT-SHOCK trial, which demonstrated that in patients with multivessel coronary disease, culprit lesion only treatment was associated with lower 30-day mortality (OR 0.84) and a reduced need for renal replacement therapy (OR 0.71) compared to complete revascularization of all angiographically significant lesions[23].

Accurate and comprehensive monitoring of patients with CS is of paramount importance, given the inherently unpredictable clinical course and high mortality associated with this condition. According to expert consensus recommendations, all patients should have an arterial line placed for continuous invasive blood pressure monitoring. A low diastolic pressure measured via this route, in the absence of bradycardia, suggests a loss of arterial tone and warrants initiation or escalation of inotropic therapy. Serial plasma lactate measurement should be performed, provided that adrenaline is not used as an inotropic agent, as lactate serves as a reliable marker of tissue (hypo)perfusion during treatment. In addition, periodic assessment of organ function markers, particularly hepatic and renal parameters, is advised. Regular determination of central venous oxygen saturation (ScvO2) is recommended, while measurement of mixed venous oxygen saturation (SvO2)—obtained from the pulmonary artery and requiring right heart catheterization—should be reserved for cases of refractory shock. Right heart catheterization itself carries only a weak recommendation and is primarily indicated in patients with refractory shock and right ventricular dysfunction. Conversely, measurement of central venous pressure (CVP) is discouraged, because it has limited accuracy and does not reliably reflect cardiac preload. Echocardiography should be performed to identify the underlying cause of shock, assess hemodynamic status, and detect mechanical complications such as cardiac tamponade[24].

Early revascularization remains the cornerstone of therapy in CS; however, pharmacologic modulation of vascular tone and myocardial performance through vasoactive agents represents an equally critical determinant of hemodynamic stabilization. Vasoactive agents are typically classified according to their predominant pharmacodynamic profile into three principal categories: inopressors (which increase cardiac index while inducing vasoconstriction), vasopressors (which elevate arterial blood pressure primarily through vasoconstriction and increased systemic vascular resistance, without direct inotropic stimulation), and inodilators (which augment cardiac output while promoting vasodilation).

The administration of these agents is exceedingly common among critically ill patients: approximately one quarter of all patients in intensive care units receive at least one inotropic agent, while in CS this proportion exceeds 90%. A large-scale study encompassing over 10,000 patients treated in a tertiary cardiac intensive care unit demonstrated a clear trend toward increased norepinephrine use, accompanied by a gradual decline in dopamine administration. In that cohort, inotropic therapy was employed in 24.7% of all admissions.

A widely used parameter for quantifying the cumulative inotropic and vasoactive burden is the Vasoactive–Inotropic Score (VIS**)**, which is defined as the sum of the maximal doses of all vasoactive agents administered, adjusted for their equipotent potencies. For example, 0.2 μg/kg/min of norepinephrine is considered equivalent to 20 μg/kg/min of dopamine. Thus, a patient receiving both agents concurrently at these doses would have a VIS of *0.2 × 100 (norepinephrine) + 20 × 1 (dopamine) = 40*, representing a high level of pharmacologic circulatory support.

In our patient, norepinephrine was administered as the sole vasoactive agent, reaching a maximal infusion rate of 0.35 μg/kg/min, corresponding to a VIS of 35. Elevated VIS values have been consistently shown to represent an independent adverse prognostic indicator, as the need for higher inotropic support reflects greater underlying disease severity.Among patients receiving vasoactive therapy in the aforementioned cohort—after adjustment for disease severity and VIS—norepinephrine use was associated with significantly lower mortality (OR 0.66)[25]. The SOAP II trial, which randomized 1,679 patients with shock of various etiologies to norepinephrine or dopamine, found no difference in overall mortality; however, dopamine administration was associated with a higher incidence of arrhythmic events (24.1% vs. 12.1%). In the subgroup of 280 patients with cardiogenic shock, dopamine use correlated with a significantly higher mortality rate[26]. The OPTIMA CC study compared epinephrine and norepinephrine in patients with cardiogenic shock following acute myocardial infarction. No difference was observed in the doses required to achieve target mean arterial pressure, hemodynamic parameters were comparable between groups. Nevertheless, epinephrine administration resulted in significantly higher lactate levels and a more pronounced metabolic acidosis. Moreover, epinephrine produced a greater increase in heart rate and in the rate–pressure product, a surrogate of myocardial oxygen consumption. The study was terminated prematurely due to the frequent occurrence of refractory shock among epinephrine-treated patients (OR 8.24)[27].

The most plausible pathophysiological explanation for the superior clinical performance of norepinephrine compared to other vasoactive agents lies in its effect on myocardial oxygen consumption. Oxygen consumption is a critically important determinant of myocardial metabolism, particularly under conditions of arterial occlusion and severely compromised coronary perfusion, as

observed in cardiogenic shock. It has been well established that heart rate exerts the greatest influence on myocardial oxygen demand. Estimates suggest that variations in heart rate account for approximately 50–70% of total myocardial oxygen consumption[28,29]. By contrast, increases in myocardial contractility during stress or elevated workload contribute an additional 15–25%[28]. Unlike most other inotropic agents, norepinephrine exerts minimal chronotropic effects, and thus only modestly elevates myocardial oxygen consumption in already ischemic regions. This pharmacodynamic profile promotes a more favorable balance between myocardial oxygen supply and demand in patients with cardiogenic shock.

Based on this physiological rationale, American guidelines recommend norepinephrine as the first-line vasoactive agent in the management of CS accompanied by hypotension (mean arterial pressure <65 mmHg). If hypotension persists despite norepinephrine administration, vasopressin may be considered as an adjunct. In cases where blood pressure stabilizes but low stroke volume persists, the addition of an inodilator (such as milrinone or dobutamine) is advisable. Conversely, in patients who are not initially hypotensive but present with a low stroke volume, an inodilator may be initiated first, with norepinephrine added subsequently if hypotension develops during the course of treatment[30].

At every stage of management—particularly in cases of refractory CS—mechanical circulatory support may be employed. The intra-aortic balloon pump (IABP) remains the most frequently used device owing to its relative simplicity, while extracorporeal membrane oxygenation (ECMO) and microaxial flow pumps (Impella) are utilized less commonly. However, meta-analyses of mechanical support in CS following AMI have failed to demonstrate a significant reduction in 30-day mortality with any modality[31]. The DANGER-SHOCK trial represents the first randomized multicenter study to demonstrate a clear survival benefit of mechanical circulatory support in AMI related CS. Among 355 patients, treatment with the Impella CP microaxial flow pump was associated with improved 6-month survival compared to standard medical therapy (OR 0.74). This benefit, however, was accompanied by a higher incidence of adverse events, including increased requirements for renal replacement therapy (OR 1.98), moderate-to-severe bleeding (OR 2.06), limb ischemia (OR 5.15), and sepsis (OR 2.76). The number needed to harm (NNH) for Impella CP use was 6. In our case, none of the above-mentioned modalities of mechanical circulatory support were available.

Conclusion

Early presentation of the patient to a PCI-capable center and prompt culprit lesion revascularisation combined with the judicious use of inotropic agents and comprehensive supportive care in an intensive care unit setting and under continuous hemodynamic monitoring can significantly improve outcomes in patients with AMI complicated with CS.

References

1. Van Diepen S, Katz JN, Albert NM, et al. American Heart Association Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Mission: Lifeline. Contemporary management of cardiogenic shock: a Scientific Statement from the American Heart Association. *Circulation* 2017;136:232-68.
2. Sinha et al. Evaluation and Management of Cardiogenic Shock. *JACC* 2025;85(16):1618-41.
3. Aissaoui N, Puymirat E, Delmas C, et al. Trends in cardiogenic shock complicating acute myocardial infarction. *Eur J Heart Fail* 2020;22(4):664–72.
4. Thiele H, thiele SdW, Freund A, et al. Management of cardiogenic shock. *EuroIntervention* 2021;17(6):
5. Jentzer, J.C. Ahmed, A.M. Vallabhajosyula, et al. Shock in the cardiac intensive care unit: changes in epidemiology and prognosis over time. *Am Heart J* 2021;232:94-104.
6. Sinha SS, Rosner CM, Tehrani BM et al. Cardiogenic shock from heart failure versus acute myocardial infarction: clinical characteristics, clinical course, and 1 year outcome. *Circ. Hearth Fail* 2022(15).
7. Bhatt AS, Berg DD, Bohula, et al. De novo vs acute on chronic presentations on heart failure related cardiogenic shock: insights from the critical care cardiology trial network registry. *J Card Fail* 2021;27:1073-81.
8. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit: a two year experience with 250 patients. *Am J Cardiol* 1967;20: 457-64.
9. McManus DD, Gore J, Yarzebski J, Spencer F, Lessard D, Goldberg RJ. Recent trends in the incidence, treatment, and outcomes of patients with STEMI and NSTEMI. *Am J Med* 2011;124:40-47.
10. Samski MD, Morrow DA, Proudfoot AG, et al. Cardiogenic shock after myodardial infarction: a review. JAMA 2021;326:1840-50.
11. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. SHOCK Investigators. Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock. *N Engl J Med* 1999; 341(9):625-34.
12. Webb JD, Slleper LA, Buller CE, et al. Implications of the timing of onset of cardiogenic shock after acute myocardial infarction: a report from the SHOCK Trial Registry. *JACC* 2000;36(3):1084-90.
13. Yang C, Lee T, Kochan A, et al. Prehospital Prediction of Cardiogenic Shock Among Patients With ST-Segment–Elevation Myocardial Infarction: The EARLY SHOCK Score. *JAHA* 2025;14(19).
14. Goldberg RJ, Spencer FA, Fox, KAA, et al. Prehospital delay in patients with acute coronary syndromes (from the Global Registry of Acute Coronary Events [GRACE]) *Am J Cardiol* 2009; 103:598-603.
15. Shi O, Khan AM, Rezai MR, et al. Factors associated with door-in to door-out delays among ST-segment elevation myocardial infarction (STEMI) patients transferred for primary percutaneous coronary intervention: a population-based cohort study in Ontario, Canada. *BMC Cardiovasc Disor* 2018;18:1-9.
16. Lawesson SS, Isaksson RM, Ericsson M, et al.Gender disparities in first medical contact and delay in ST-elevation myocardial infarction: a prospective multicentre Swedish survey study. *BMJ Open* 2018;8:1-10.
17. Libungan B, Karlsson T, Hirlekar G, et al. Delay and inequality in treatment of the elderly with suspected acute coronary syndrome. *Int J Cardiol* 2014;176:946-50.
18. Nguyen HL, Gore JM, Saczynski JS, et al. Age and sex differences and 20-year trends (1986 to 2005) in prehospital delay in patients hospitalized with acute myocardial infarction. *Circ-Cardiovasc Qual* 2010;3:590-8.
19. Jolic A, Mitov V, Adamovic D, Dimitrijevic M, Nikolic M. The specificities of eastern Serbia STEMI network organization during 2020 COVID year. *Srce i krvni sudovi* 2022;41(3): 57-60
20. Forrester J, Diamond G, Chatterjie K. Medical therapy of acute myocardial infarction by application of hemodynamic subsets. (first of two parts) *N Engl J Med* 1976;295:1356-62
21. Forrester, J · Diamond, G · Swan, H. Correlative classification of clinical and hemodynamic function after acute myocardial infarction. *Am J Cardiol.* 1977;39:137-54

22. Forrester, J.S., Diamond, G., Chatterjee, K., et al. Medical therapy of acute myocardial infarction by application of hemodynamic subsets (second of two parts). *NEJM* 1976;295: 1404-13.
23. Thiele H, Akin I, Sandri M, et al. PCI Strategies in Patients with Acute Myocardial Infarction and Cardiogenic Shock. *NEJM* 2017; 377(25):2419-32.
24. Levy B, Bastien O, Bendjelid K, et al. Experts' recommendations for the management of adult patients with cardiogenic shock. *Ann Intensive Care* 2015;5:17.
25. Jentzer JC, Wiley B, Bennett C, et al. Temporal trends and clinical outcomes associated with vasopressor and inotrope use in the cardiac intensive care unit. *Shock* 2020;53:452–9.
26. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362:779–89.
27. Levy B, Clere-Jehl R, Legras A, et al. Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. *J Am Coll Cardiol*. 2018;72:173–82.
28. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. *Physiol Rev* 2008;88:1009–86.
29. Sonnenblick EH, Braunwald E, Williams JF, Glick G. Effects of exercise on myocardial force velocity relations in intact unanesthetized man: relative roles of changes in heart rate, sympathetic activity, and ventricular dimensions. *J Clin Invest*. 1965;44:2051–62.
30. Bloom JE, Chan W, Kaye DM, et al. State of Shock: Contemporary Vasopressor and Inotrope Use in Cardiogenic Shock. *JAHA* 2023; 12(15)
31. Neves HA, Romaniello G, Collini M, et al. Mechanical Circulatory Support in Cardiogenic Shock Secondary to Acute Myocardial Infarction: A Systematic Review and Network Meta-analysis of Randomized Controlled Trials. *Circulation* 2024;150(1).

Sažetak

Perkutana koronarna intervencija kod pacijenta sa kardiogenim šokom u centru bez mogućnosti mehaničke cirkulatorne potpore: Prikaz slučaja i pregled postojeće literature

Nikolić Milan[1], Mitov Vladimir[1], Jolić Aleksandar[1], Adamović Dragana[1], Nikolić Milena[2]

[1]Odeljenje Invazivne Kardiologije, Zdravstveni Centar Zaječar, [2]Odeljenje Anesteziologije i Reanimacije; Zdravstveni Centar Zaječar

***Uvod**: Kardiogeni šok je jedno od najtežih stanja u kardiološkoj jedinici intenzivne nege sa kratkoročnim mortalitetom 30-40%. Predstavlja sindrom hipoperfuzije i disfunkcije organa zbog primarno srčanog uzroka, najčešće kao posledica akutnog infarkta miokarda.*

***Cilj rada**: Prikaz bolesnice odmakle životne dobi lečene pod slikom kardiogenog šoka nakon akutnog infarkta miokarda u PCI centru bez mogućnosti primene mehaničke cirkulatorne potpore.*

***Prikaz slučaja**: Bolesnica starosti 85 godina primljena je na Odeljenje invazivne kardiologije ZC Zaječar sa slikom STEMI anteriorne lokaliazacije 9h nakon početka bola u grudima i razvijenim kardiogenim šokom klase III po Foresteru. Urađena je primarna PCI LAD nakon čega je lečena intortopnom potporom noradrenalinom u maksimlanoj dozi od 0.34 mcg/kg/min uz opreznu infuziju kristaloidnih rastvora i ostalu terapiju srčane insuficijencije. Na primenjenu terapiju dolazi do hemodinamske stabilizacije i isključenja inotropne stimulacije i pored teške sistolne disfunkcije leve komore sa EF 15-20% i teške mitralne regurgitacije. Dalji tok bolesti komplikovan je aspiracionom pneumonijom, dijarealnim sindromom i d*

*ehidratacijom sa hipernatrijemijom i naposletku smrtnog ishoda nakon 21 dana lečenja. **Zaključak**: Hitna primarna PCI procedura u najbližem PCI centru uz davanje inotropnih lekova i druge suportivne mere u kardiološkoj jedinici intenzivnog lečenja može dovesti do hemodinamske stabilizacije i veoma teških bolenika odmakle životne dobi sa kardiogenim šokom.*

***Ključne reči**: akutni infarkt miokarda, STEMI, kardiogeni šok, inotropni lekovi, noradrenalin*

Srce i krvni sudovi 2025; 44(3) : 122-127

Case report

In-stent restenosis: neointimal priliferation or neoatherosclerosis

Vladimir Mitov[1], Aleksandar Jolić[1], Vladimir Zdravković[2], Milan A Nedeljković[3], Vladan Vukčević[3], Siniša Stojković[3], Milan Nikolić[1], Dragana Adamović[1], Igor Tomas[4], Mirjana Krkić[5]

[1]Department of Interventional cardiology, Medical center Zaječar, [2]Cardiology Clinic, Clinical center Kragujevac, [3]Cardiology Clinic, Clinical center Srbije, [4]Cardiology Clinic, ICVD Sremska kamenica, [5]Department of Interventional cardiology, Medical center Kruševac

Abstract In-stent restenosis, according to the time of occurrence presents itself as: earlywithin 24 hours; subacutewithin the first month; latewithin the first year; and very lateafter the first year.
A 72yearold female patient, D.Đ., was referred for rescue PCI (Percutaneous Coronary Intervention) after fibrinolysis for anteriorwall STEMI. Coronary angiography showed subocclusive lesions in the Cx (Circumflex artery) and LAD (Left Anterior Descendent), as well as a significant lesion in the RCA (Right Coronary Artery). A Synergy 3×16 stent at 12 atm was placed in the Cx, and a Synergy 3.5×16 stent at 10 atm in the LAD.
After six months, she was re-hospitalized for anterior-wall NSTEMI (Non-ST Elevation Myocardial Infarction). Coronary angiography revealed in-stent restenosis in the Cx and LAD, which were treated with post-dilatation using an NC Mozec 3.5×18 balloon.
Four months later, recurrent chest pain occurred. Coronary angiography showed subocclusive restenosis in the Cx. IVUS (Intravascular Ultrasound) demonstrated the presence of calcium behind the stent and neointimal proliferation within the stent. IVL (Intravascular Lithotripsy) was performed with a 3.5×15 balloon for 4 cycles. A DEB (Drug-Eluting Balloon) Elutax 3.5×20 was applied to the stent and proximal Cx for 55 seconds.
After eight months, another coronary angiography was performed due to reoccurring chest pain and a subsequent positive exercise stress test. Coronary angiography again showed a subocclusive lesion in the Cx stent, managed with a 3.5×16 NC balloon. Due to recurrent in-stent restenosis despite successful calcium removal with IVL and the presence of neointimal proliferation seen on IVUS, colchicine 0.5 mg daily was added for one year.
After one year, control coronary angiography again revealed in-stent restenosis in the Cx. Repeat IVUS this time demonstrated a small thrombus and areas of neoatherosclerosis as the mechanism of restenosis. Due to the neoatherosclerotic changes, the in-stent stenosis was treated with repeated IVL using a 3.5×15 balloon for all 12 cycles, and implantation of a new Synsiro 3.5×15 stent.
In-stent restenosis, based on the timing of presentation, may be acute, subacute, late, or very late. Mechanisms of in-stent restenosis, according to the time of onset, may include thrombosis, neointimal proliferation, and neoatherosclerosis. Regardless of timing, therapeutic approaches include balloon dilatation, application of a DEB, or implantation of a DES. Only in cases of proven neointimal proliferation additional oral therapy with colhicine, methotrexate or sirolimus should be considered, or parenteral administration of paclitaxel.

Key-words In-stent restenosis, thrombosis, neointimal proliferation, neoatherosclerosis

Introduction

In-stent restenosis has been a persistent issue since the introduction and use of stents. With the advent of new-generation stents made from improved alloys, with thinner struts and higher-quality polymers carrying antiproliferative drugs, this problem has become significantly less commonnow occurring in about 2% of implanted stents in the left main coronary artery after 2 years of follow-up[1], or 0.8% in patients with DES and 1.2% (P = 0.0498) in patients with BMS after 6 years of follow-up[2].

In-stent restenosis, based on the time of onset, can be classified as: **Early-**within 24 hours; **Subacute-**within the first month; **Late-**within the first year; and **Very late-**after the first year.The development of in-stent restenosis is influenced by patientrelated factors such as stent implantation during ACS (Acute Coronary Syndrome) or premature discontinuation of DAPT (Dual Antiplatelet Therapy). Other patient related factors, like diabetes mellitus, age, smoking, malignancy, heart failure, and renal failure directly or indirectly contribute to accelerated atherosclerotic processes in the coronary vessels

Corresponding author: Vladimi Mitov, MD, PhD, drvladimirmitov@gmail.com

Table 1. Classification and factors influencing the development of in-stent restenosis

Type	Time Line	Factors from the patients	Factors from the lesion	Factors from the procedure
Acute	Within 24h	ACS-STEMI	Small vessel diameter	Residual dissection
Subacute	Within 30 days	Diabetes mellitus	Long lesion	Impropriate stent expansion
Late	After 30 days	Heart failure	Bifurcation lesion	Stent malposition
Very Late	After 1 year	Chronic kidney failure	CTO	Stents overlap
		Aging	Thrombosis	>30mm stents
		Smoking	Vein graft lesion	BMS/DES
		DAPT interruption		Stent design
		Malignancy		Drugs at the stent

ACS-STEMI-Acute Coronary Syndrome-ST Elevation Myocardial Infarction, CTO-Chronic Total Oclusion, BMS-Bare Metal Stent, DES-Drug Eluting Stent, DAPT Dual AntyPlateTherapy. Taken and adapter from(3).

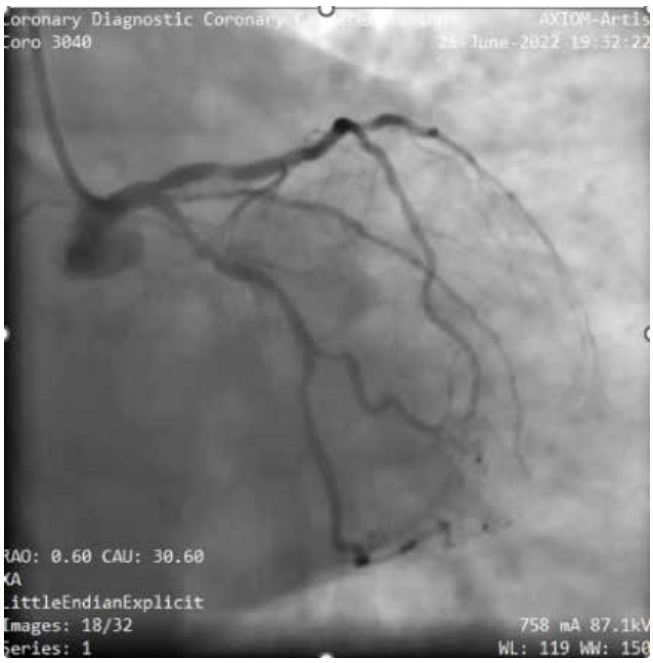


Figure 1a. Coronary angiography of the Cx (Circumflex artery) and LAD (Left Anterior Descending artery);

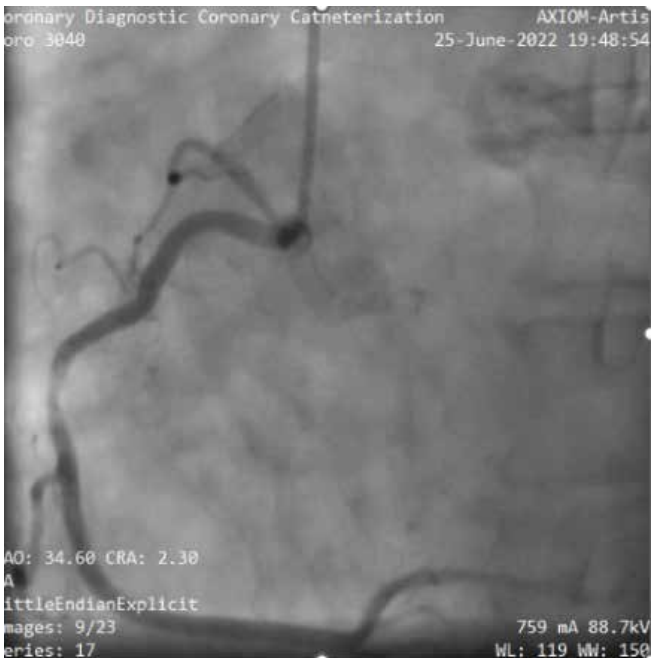


Figure 1b. Coronary angiography of the RCA (Right Coronary Artery).

and within the stent itself.Lesion-related factors include small vessel diameter, long lesions, bifurcation lesions, CTO (Chronic Total Occlusion), thrombosis, or lesions in vein graftsthat is, lesions requiring multiple stents; complex stent implantation procedures; the use of long stents or stents of smaller diameter, both of which are known to be more prone to thrombosis.Procedurerelated factors include inadequate stent positioning, overlap, or expansion; residual dissectionwhich is often unrecognized; the use of long stents; specific stent designs-especially oldergeneration devices with thicker struts; or the type of polymer and drug used in the stent (Table 1).

In recent years, intravascular imaging has become increasingly accessible and widely used, providing new informationnot only a quantitative assessment of the amount of tissue within the stent that partially or completely compromises blood flow, but also a qualitative assessment of the type of changes within the vessel or within the vessel wall, such as neointimal proliferation or neoatherosclerosis, with or without calcification[4].

Aim of the study

Presentation of case report which would highlight the important clinical dilemma of whether distinguishing neointimal proliferation from neoatherosclerosis as mechanisms of in-stent restenosis has significant therapeutic implications.

Case report

A 72-year-old female patient, D.Đ., was referred for rescue PCI after fibrinolysis for anterior-wall STEMI. On admission, signs and symptoms of heart failure were present. Her past medical history included chronic obstructive pulmonary disease, pulmonary sarcoidosis, and breast cancer. **Coronary angiography** showed suboclusive lesions in the Cx and LAD, as well as a significant lesion in the RCA (Figures 1a and 1b).

Given that this was a rescue PCI in the presence of heart failure, it was decided to treat the Cx and LAD. A Synergy 3×16mm stent at 12 atm was implanted in the Cx, and a Synergy 3.5×16mm at 10 atm in the LAD. The patient was on optimal medical therapy.

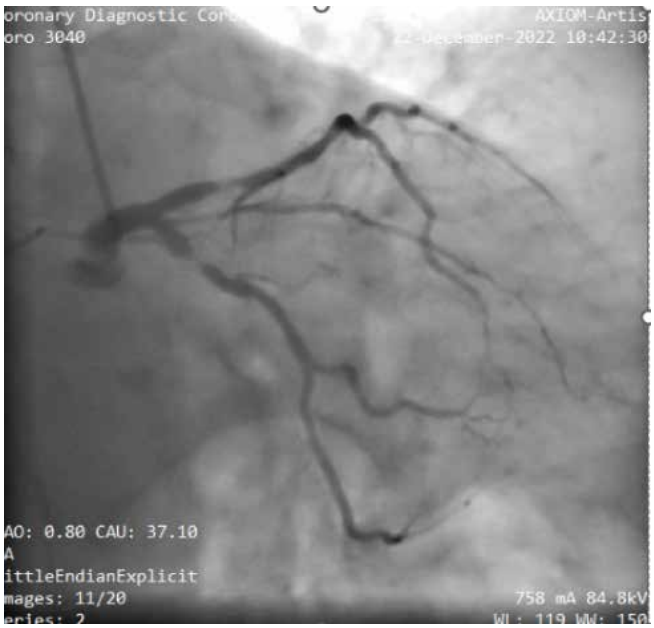


Figure 2. Coronary angiography showing in-stent restenosis of the Cx and LAD.

After six months, the patient was re hospitalized for anteriorwall NSTEMI. Coronary angiography revealed in-stent restenosis in the Cx and LAD (Figure 2). Both were treated with post-dilatation using an NC Mozec 3.5×18 balloon.

Four months later, the patient develops anginal pain again. Coronary angiography showed subocclusive restenosis in the Cx (Figure 3a). IVUS demonstrated calcium behind the stent and neointimal proliferation within the stent (Figure 3b). Because of the calcium behind the stentvisible on fluoroscopy during angiography-and inadequate stent expansion as a possible mechanism of restenosis, IVL was performed with a 3.5×15 balloon for 4 cycles. A DEB Elutax 3.5×20 was applied to the stent and proximal Cx for 55 seconds.

After eight months, another coronary angiography was performed due to chest pain and a positive exercise test. It revealed a subocclusive lesion in the Cx stent (Figure 4), which was treated with a 3.5×16 NC balloon.

Because of recurrent multiple in-stent restenosis, despite successful calcium removal by IVL and the presence of neointimal proliferation seen on IVUS, colchicine 0.5 mg daily was added for the next 12 months.

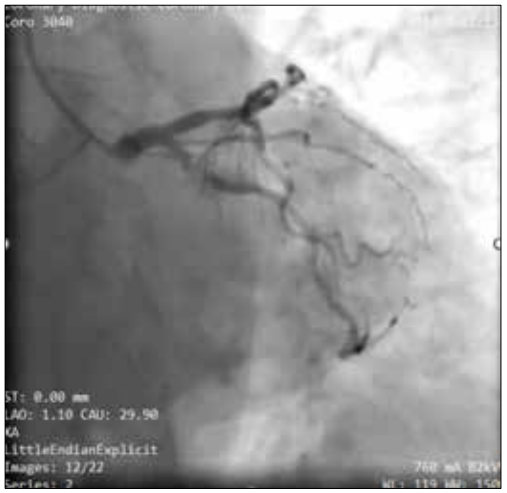


Figure 3a. Coronary angiography with in-stent restenosis in the Cx;

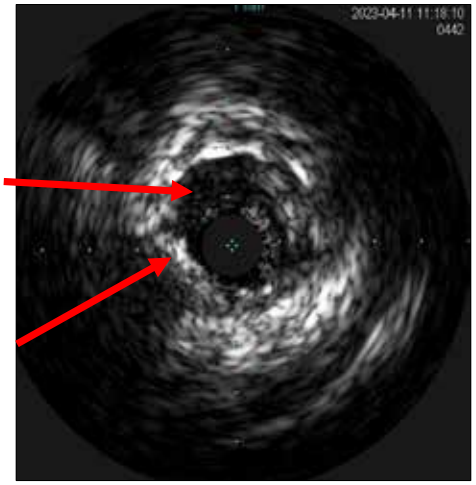


Figure 3b. IVUS demonstrating in-stent restenosis in the Cx (neointimal proliferation).

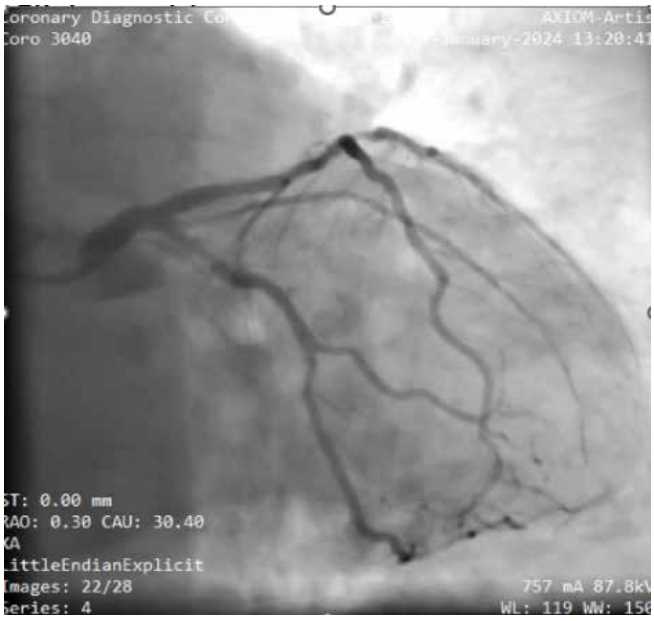


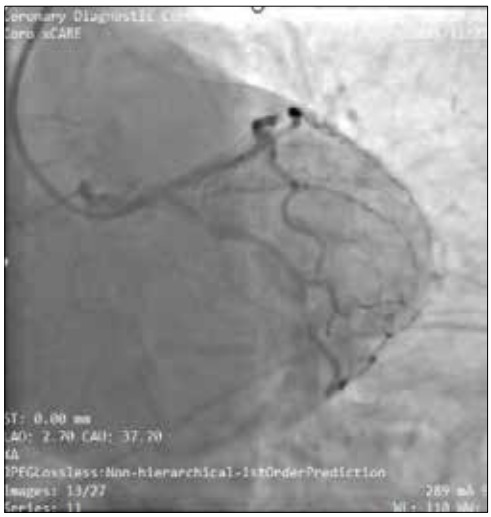
Figure 4. In-stent restenosis in the Cx.

After 12 months control coronary angiography again showed in-stent restenosis in the Cx (Figure 5a).

Repeat IVUS now demonstrated a small thrombus and areas of neoatherosclerosis as the mechanism of restenosis (Figure 5b). As there was no new neointimal proliferation, colchicine was discontinued. Due to the neoatherosclerotic changes, the instent stenosis was treated with repeat IVL using a 3.5×15 balloon for all 12 cycles and implantation of a new Synsiro 3.5×15 stent. Throughout treatment, the patient remained on optimal DAPT and intensive lipid-lowering therapy with rosuvastatin 40 mg and ezetimibe 10 mg, achieving adequate cholesterol control.

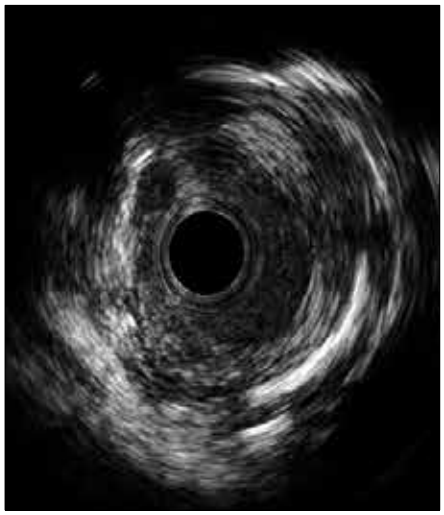
Discussion

Instent restenosis is rare but still present, even with new stent designs and modern drugeluting polymers. According to Waksman[5], mechanisms of in-stent resteno-



Thrombus

Figure 5a. In-stent restenosis in the Cx.



Neoateroclerosis

Figure 5b. IVUS showing restenosis due to neoatherosclerosis.

Table 2. Waksman In-Stent Restenosis Classification[5].

Type	Definition		Treatment Options
I	Mechanical	Underexpansion (Type I A)	High-pressure balloon
		Stent fracture (Type I B)	DES
II	Biologic	Intimal hyperplasia (Type II A)	Balloon, DEB, DES, and VBT
		Neoatherosclerosis, noncalcified (Type II B)	DCB and DES
		Neoatherosclerosis, calcified (Type II C)	Scoring balloon, ELCA, and RA
III	Mixed pattern: Combined mechanical and biologic etiology		High-pressure balloon with DEB, DES, or VBT
IV	Chronic total occlusion		DCB or DES, VBT for multiple layers, CABG as needed
V	>2 layers of stent		Balloon, DCB, VBT, and CABG

DES—drug-eluting stent; DEB—drug-eluting balloon; ELCA—excimer laser coronary atherectomy; RA—rotational atherectomy; VBT—vascular brachytherapy; CABG—coronary artery bypass graft.

sis may be mechanical (due to under expansion or stent fracture), biological (neointimal proliferation, neoatherosclerosis with or without calcification), combined (mechanical + biological), CTO, or involvement of more than two stent layers (Table 2).

When assessed along a timeline, **acute** (<24 h) and **subacute**(<1 month) restenoses almost always result from instent **thrombosis** due to malposition, underexpansion or stent fracture. These are typically resolved with balloon dilatation (Table 3).

However, in our experience, **late restenosis** (within 1 year) may be caused by neointimal proliferation or neoatherosclerosis. Treatment involves balloon dilatation followed by local drug delivery via DEB or placement of a new stent. The remaining question is whether this approach is appropriate in cases of neointimal proliferation. Pathophysiologicaly, **neointimal proliferation** results from endothelial cell dysfunction caused by stretching and pressure appliance during balloon dilatation and stent implantation. Endothelial activation triggers a cascade of mechanisms leading to proliferation:

1. Disturbed nitric oxide (NO) release in endothelial cells occurs within hours of mechanical stretch.

2. Platelet activation, contributing to instent thrombosis, also occurs within hours.

3. Inflammatory activation as a mechanism that occurs in the first days, leads to the activation of inflammatory cells.

Table 3. Types of in-stent restenosis, mechanisms of occurrence, and therapeutic options.

Type	Time Line	Mehanism	Therapy 1st Line	Therapy 2nd Line	Devices Therapy
Acute	Within 24h	Thrombosis	DAPT		Balloons (NC), DEB, DES
Subacute	Within 30 days	Thrombosis	DAPT		Balloons (NC), DEB, DES
Late	After 30 days	Neointimal proliferation	DAPT Statins	Colchicine MTx Sirolimus Paclitaxel	Balloons(NC, Scoreflex), DEB, DES, VBT
Very Late	After 1 year	Neoatherosclerosis	Statins		Balloons(NC, Scoreflex), DEB, DES, CABG

DAPT—Dual Antiplatelet Therapy; NC—Noncompliant; DEB—Drug-Eluting Balloon; DES—Drug-Eluting Stent; MTx—Methotrexate; VBT—Vascular Brachytherapy; CABG—Coronary Artery Bypass Graft.

Subsequent mechanisms that are activated and last for weeks and months lead to structural disorders in the thickness of the blood vessel wall.

4. Matrix metalloproteinase activation degrades elastin and collagen in the tunica media, enabling migration of smooth muscle cells into the intima[6]. There, smooth muscle cells transform phenotypically into secretory cells that producing mediators: growth factors, proteases, and inflammatory mediators, which drive neointimal proliferation.

According to Zain, neointimal proliferation may be *Arterial* as an endothelial response to endarterectomy or PCI, *Venous* as an endothelial response to CABG. After the first year, venous grafts undergo arterialization, and after year five, lumen reduction is primarily due to neoatherosclerosis[7].

Since the mechanism of neointimal proliferation is vesselwall stretch, the question arises whether additional balloon dilatation or new stent implantation is beneficial. Neointimal proliferation occurs within the first year, when DES still releases active cytostatic drug[8]. Therefore, local therapy via DEB plus systemic antiproliferative therapyoral or parenteralmay be preferable (Table 3). In the future, newgeneration bioresorbable scaffolds may play a role in first year fortreatment instent restenosis.

In our case, based on the COLCOT and LoDoCo2 trials and current guidelines[9], colchicine 0.5 mg daily was prescribed for 12 months. After one year, restenosis recurred but was identified by IVUS as neoatherosclerotic rather than neointimal. It remains unclear whether this systemic therapy effectively treats neointimal proliferation. Vascular brachytherapy is proposed as a lastline option (Table 3).

Very late restenosis (after 1 year) is caused by **neoatherosclerosis** the development of atherosclerotic changes within the neointima after stent implantation. It is characterized by inflammation, macrophages or foam cells phagocytosed lipids and cholesterol crystals. As with native atherosclerosis, a lipid pool is formed, in which a necrotic core usually appears[10]. The presence of a necrotic core is the basic substrate for calcium deposition, and it depends on whether neoatherosclerosis with calcification or without calcification will develop. Calcium in neoatherosclerosis is usually superficial and focal in the form of nodules, rarely deep and diffuse. In our case, IVUS demonstrated thrombus and neoatherosclerosis within the stent. This slow process develops over many years and can continue long term. It is treatable with balloon dilatation, local drug application (DEB), or repeat stenting (Table 3).

Conclusions

Instent restenosis, based on timing, may be acute, subacute, late, or very late. Its mechanisms include thrombosis, neointimal proliferation, and neoatherosclerosis. Regardless of timing, treatment involves balloon dilatation, use of DEB, or implantation of a DES. Only in cases of confirmed neointimal proliferation should additional therapy be consideredoral colchicine, methotrexate or sirolimus, or parenteral paclitaxel.

References

1. Byrne R.A, Fremes S, Capodanno D, et al. 2022 Joint ESC/EACTS review of the 2018 guideline recommendations on the revascularization of left main coronary artery disease. European Heart Journal (2023) 44, 4310–4320.
2. Bønaa KH, Mannsverk J, Wiseth R, et al. NORSTENT Investigators. Drug-eluting or bare-metal stents for coronary artery disease. N Engl J Med 2016;375:1242–1252. doi: 10.1056/NEJMoa1607991.
3. Damjanović M, Pavlović M, Apostolović S. Prevencija tromboze stenta. Srce i krvni sudovi 2014; 33(2):123-127.
4. Hassani NS, Ogliari LC, de Oliveira Salerno PRV, et al. In-Stent Restenosis Overview: From Intravascular Imaging to Optimal Percutaneous Coronary Intervention Management. Medicina 2024; 60:549. https://doi.org/10.3390/medicina60040549.
5. Waksman R, White RL, Chan RC, et al. Intracoronary gamma-radiation therapy after angio plasty inhibits recurrence in patients with in-stent restenosis. Circulation 2000; 101:2165–2171. doi: 10.1161/01.cir.101.18.2165.
6. Melnik T, Jordan O, Corpataux JM, et al.Pharmacological prevention of intimal hyperplasia: A state-of-the-art review. Pharmacology & Therapeutics 2022; 235: 108157.
7. Zain MA,. Jamail RT., Siddiqui WJ. Neointimal Hyperplasia. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.
8. Taniwaki M, Häner JD, Kakizaki R, et all. Long-term effect of biodegradable vs. Durable polymer everolimus-eluting stents on neoatherosclerosis in ST-segment elevation myocardial infarction: the CONNECT trial. Eur Heart J 2025; 46:2906–2916 https://doi.org/10.1093/eurheartj/ehae589.
9. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Eur Heart J 2023; 44:3720–3826 ttps://doi.org/10.1093/eurheartj/ehad191.
10. Nusca A, Viscusi MM, Piccirillo F, et al. In Stent Neo-Atherosclerosis: Pathophysiology, Clinical Implications, Prevention, and Therapeutic Approaches. Life 2022; 12:393. https://doi.org/10.3390/life12030393.

Sažetak

In-stent restenoza: neointimalna proliferacija ili neoateroskleroza

Vladimir Mitov[1],Aleksandar Jolić[1], Vladimir Zdravković[2], Milan A Nedeljković[3], Vladan Vukčević[3], Siniša Stojković[3], Milan Nikolić[1], Dragana Adamović[1], Igor Tomas[4], Mirjana Krkić[5]

[1]Odeljenje Invazivne kardiologije, ZC Zaječar, [2]Klinika za kardiologiju, KC Kragujevac, [3]Klinika za kardiologiju, KC Srbije,Klinika za kardiologiju, [4]IKVB Sremska kamenica, [5]Odeljneje invazivne kardiologije ZC Kruševac

*In stent restenoza prema vremenu nastanka može biti: **Rana**-unutar 24, **Subakutna**-unutar prvog meseca, **Kasna**-unutar prve godine, **Veoma kasna**-posle prve godine. Bolesnica D.Đ., 72 godine stara upućena je na **spašavajuću PCI** (Percutaneus Coronary Intervention) nakon fibrinolize i STEMI prednjeg zida. Na koronarografiji viđene su subokluzivne lezije na Cx i LAD, kao i signifikantna lezija na RCA. Na Cx je plasiran stent Synergy 3x16 na 12 atm, na LAD Synergy 3,5x16 na 10 atm. **Nakon 6 meseci** nova hospitalizacija zbog NSTEMI (Non ST Elevation Myocardial Infarction) prednjeg zida. Urađena je rekoronarografija sa in stent restenozama na Cx i LAD koje su rešene postilatacijom balonom NC Mozec 3,5x18. **Nakon 4 meseci** ponovni bol u grudima, na koronarografiji suboklu-*

zivna restenoza u Cx. Na IVUS (IntraVascular Ultra Sound) vidi se prisustvo kalcijuma iza stenta i neointimalna prliferacija u stentu. Sproveden je IVL (Intra Vascular Lithotripsy) balonom 3,5x15 na 4 ciklusa. U stent i proksimalni deo Cx plasiran je DEB (Drug Eluting Baloon) Elutax 3,5x20 u trajanju od 55 sec. ***Nakon 8 meseci*** *ponovna koronarografija zbog bola u grudima i pozitivnog ergo testa. Na koronarografiji subokluzivna lezija u stentu u Cx koja ja rešena NC balonom 3,5x16. Zbog ponavljanih in stent restenoza i nakon uklanjanja kalcijuma uspešnim IVL, i prisutne neointimalne proliferacije, viđene na IVUS, u terapiju je uveden Colhicin 0,5mg dnevno, narednih godinu dana.* ***Nakon godinu dana****, na kontrolnoj koronarografiji viđena je ponovna in stent restenoza u Cx. Na ponovnom IVUS sada se uočava prisustvo manjeg tromba i zona neoakteoskleroze kao mehanizma in stent restenoze. Zbog neoaterosklerotičnih promena, in stent stenoza je tretirana ponovnim IVL balonom 3,5x15 svih svih 12 ciklusa, i implantacijom novog stenta Synsiro 3,5x15. In stent restenoza, u odnosu na vreme nastanka, može biti akutna, subakutna, kasna, veoma kasna. U odnosu na vreme nastanka, mehanizmi in stent restenoze mogu biti tromboza, neointimalna proliferacija i neoateroskleroza. Terapijski pristup je bez obzira na vreme nastanka je balon dilatacija, primena DEB ili DES. Jedino u slučaju dokazane neointimalne proliferacije razmotriti dodatnu per os primenu Colhicina, Metotrexata, Sirolimusa ili parenteralnu primenu Paclitaxela.*

Ključne reči: *In stent restenoza, tromboza, neointimalna proliferacija, neoateroskleroza.*

Srce i krvni sudovi 2025; 44(3) : 128-132

Case report

Recurrent Percutaneous Coronary Interventions in a Patient With a Single Coronary Ostium Arising From the Right Coronary Sinus: An 18-Year Clinical Course

Oliver Kalpak[1], Nikola Manev[1], Aleksandar Jovkovski[1], Antonio Georgiev[1], Hristo Pejkov[1]

[1]University Clinic for Cardiology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, RN Macedonia

Abstract This report describes an 18-year longitudinal clinical course of a patient with a rare single coronary ostium originating from the right coronary sinus. The patient underwent percutaneous coronary intervention (PCI) with bare-metal stents (BMS) to the proximal left anterior descending artery (LAD) and proximal right coronary artery (RCA) in 2007, with complete long-term patency and no restenosis for nearly two decades.

In August 2025, he presented with non–ST-segment elevation acute coronary syndrome (NSTE-ACS) caused by a new, heavily calcified 99% mid-LAD stenosis. PCI required high-pressure plaque modification using OPN super–high-pressure balloons up to 50 atm, followed by deployment of a drug-eluting stent (DES) with an excellent angiographic result. One month later, elective PCI addressed severe proximal circumflex (LCx) stenosis and a high-grade obtuse marginal (OM) branch lesion, treated with DES and drug-eluting balloon (DEB) therapy, respectively.

This case highlights the natural history of coronary atherosclerosis in congenital coronary anomalies, the long-term durability of early-generation BMS, and the technical challenges posed by extreme calcification. It underscores the importance of lifelong surveillance and tailored revascularization strategies in patients with single-ostium coronary anatomy.

Key-words Congenital coronary vessel anomalies, single coronary artery, percutaneous coronary intervention, super-high pressure balloon, drug eluting stents

Introduction

Anatomical definition of the normal coronary circulation, as proposed by Angelini, identifies three principal vessels: the right coronary artery supplying the right ventricular free wall; the left anterior descending artery supplying the anterior interventricular septum; and the circumflex artery supplying the free lateral wall of the left ventricle[1]. The earliest anatomical depictions—including those by Leonardo da Vinci—already recognised distinct epicardial pathways.

Congenital coronary artery anomalies occur in less than 1% of the population, with a single coronary ostium representing fewer than 0.04% of cases[2-3]. A solitary ostium arising from the right coronary sinus is particularly rare and may be associated with potentially malignant interarterial courses, altered shear stress patterns, vulnerability to atherosclerotic progression, and procedural complexity during coronary intervention. Clinical outcomes in such patients depend on underlying anatomy, cumulative coronary disease burden, and the evolution of PCI technologies over time[4].

The different view point of the surgeon and interventionist compared to the imager[5]. To be clear our case anomaly was single coronary artery and retro aortic route of the LAD and Cx separated early from the short LM rising in the right sinus of Valsalva. In 1990 Yamanaka O and Hobbs updated earlier Lipton classification of Coronary artery anomalies exploring them in 126,595 patients undergoing coronary arteriography in Cleveland Clinic[2].

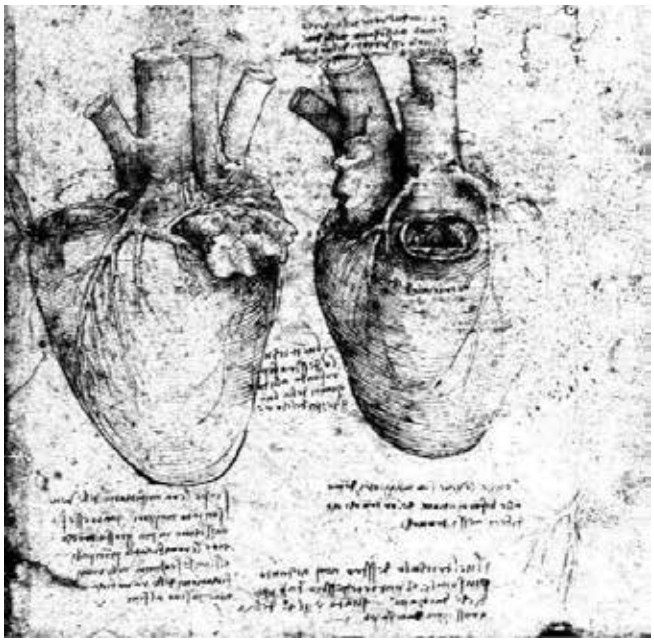


Figure 1. Leonardo da Vinci's drawings

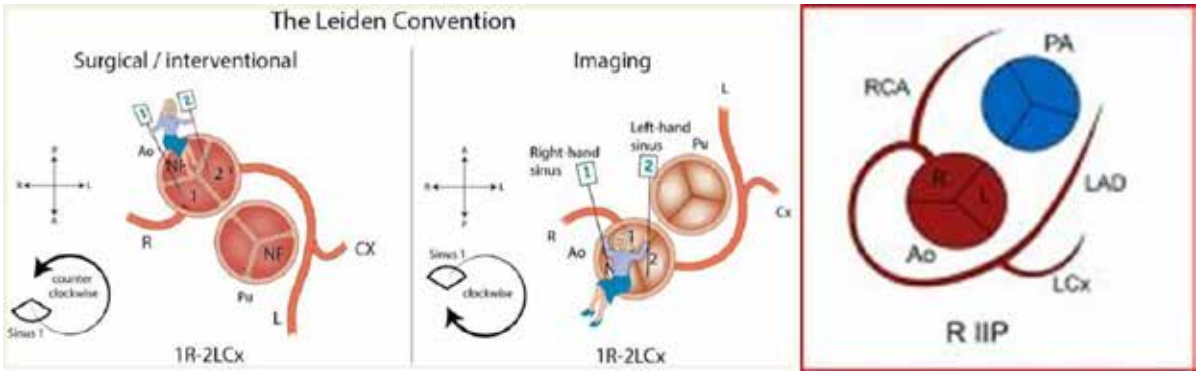


Figure 2. Leiden convention and Lipton classification

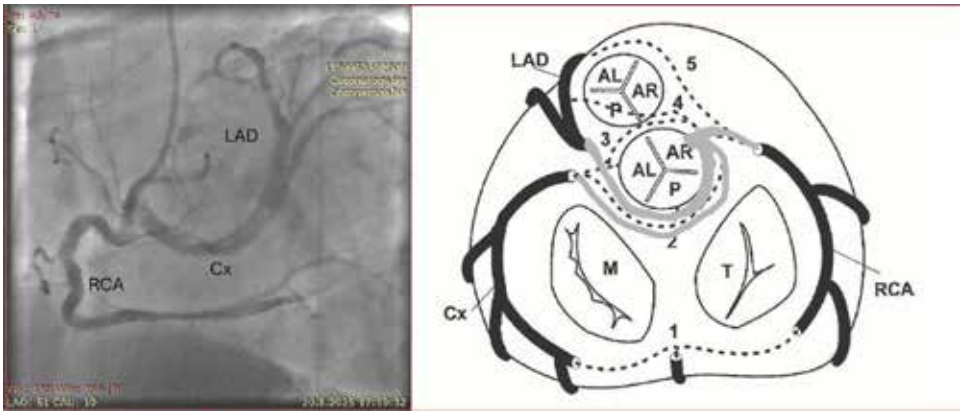


Figure 3. Our patient anatomy showing Single Coronary Artery and retro aortic path of LAD and Cx, they divide after short LM

We report the full 18-year course of a patient with a single coronary ostium from the right sinus who underwent PCI in 2007 and subsequently required two further revascularisation procedures in 2025. The case illustrates the interplay between congenital anatomy, disease progression, and modern interventional techniques.

Case Presentation

Baseline Anatomy and First PCI (2007)

A 54-year-old male with hypertension and chronic nicotine exposure underwent coronary angiography for exertional angina in 2007. At first right Judkins was unable to cannulate the ostium so we switch to Guiding Right AL2 and we engage the single ostium for whole coronary system. Imaging demonstrated a single coronary ostium in the right sinus of Valsalva, giving rise to the RCA and a short left main artery before bifurcating into the LAD and LCx with a retro-aortic course. Significant proximal stenoses of both the LAD and RCA were treated . We identify 99% stenosis of pRCA and 90% stenosis of pLAD. There were also several plaques downstream from that stenosis but at that time without clinical significance. He receive on pRCA 3.5/15 BMS on 18 atm and in the same time on pLAD one 4,0/18 BMS at 18 atmospheres of pressure. The procedure was uneventful, and the patient remained asymptomatic for years.

Long-Term Clinical Course (2007–2025)

The patient did not attend routine cardiology follow-up due to longstanding fear of hospitals. He remained asymptomatic and physically active as a manual agricultural worker. In 2025—18 years after his initial PCI—repeat angiography confirmed complete patency of both BMS without restenosis.

Acute Coronary Syndrome — August 2025 Presentation

In August 2025, the patient presented with severe chest pain and elevated troponin levels consistent with NSTE-ACS.

Angiographic Findings

Repeat angiography confirmed the unchanged single-ostium anatomy and widely patent 2007 BMS. However, a new 99% stenosis with concentric heavy calcification had developed in the mid-LAD at a site that showed only mild irregularity in 2007.

PCI Procedure

Multiple compliant and non-compliant balloons ruptured around 10 atm due to the sharp and rigid calcium. A non-compliant balloon showed a severe hourglass (“sand-clock”) waist even at 24 atm, indicating an undilatable lesion.We used many conventional tricks but effect was rather small not sufficient to proceed with stent implantation[6].
Lesion preparation required OPN super-high-pressure balloons (2.5 × 10 mm and 3.0 × 15 mm) inflated to 50 atm, resulting in partial modification and a controlled dissection without flow compromise. A 3.0 × 30 mm DES was deployed at 16 atm with optimal expansion and TIMI-3 flow. The patient was discharged the next morning.

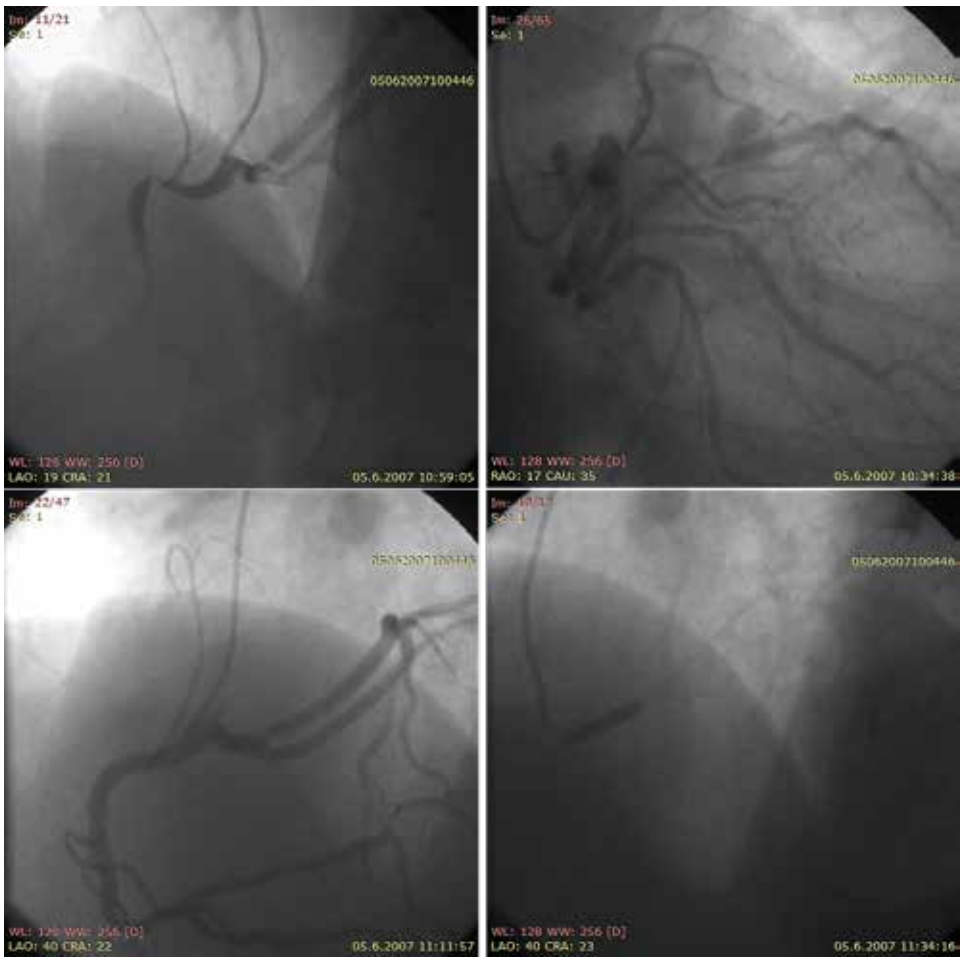


Figure 4. Our surprise

Elective PCI — September 2025

Findings

One month later, the mid-LAD DES remained patent, although with mild peri-stent contrast staining at the previously calcified segment. Additional lesions were noted:

- 90% proximal LCx stenosis
- 95% high-grade OM lesion in a small-calibre (≈2 mm) branch
- 90% diagonal branch stenosis (asymptomatic; preserved flow)

The LCx lesion was treated with a new-generation DES. The OM lesion was treated with DEB angioplasty due to its small diameter. The diagonal branch lesion was left untreated because the patient was asymptomatic with good flow.

Discussion

1. Durability of Early-Generation BMS

The 2007 BMS remained widely patent after 18 years, with only mild (<30%) restenosis in the RCA. Such long-term durability, though uncommon, has been documented in specific anatomical and procedural contexts.

2. Progression of Native-Vessel Atherosclerosis

The patient developed severe calcific disease in the mid-LAD rather than in-stent restenosis. Single-ostium coronary anatomy may alter shear stress distribution, predisposing to progressive calcification.

3. Challenges in Treating Extreme Calcification

Conventional non-compliant balloons failed at pressures well above their rated limits. OPN balloons provided the necessary plaque modification and illustrate their value in focal, heavily calcified lesions, particularly when ana-

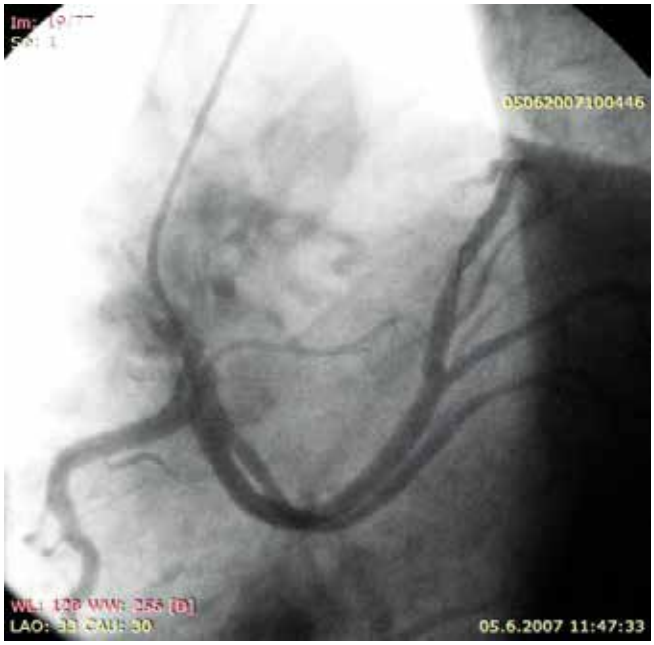


Figure 5. Final image after the procedure (2007)

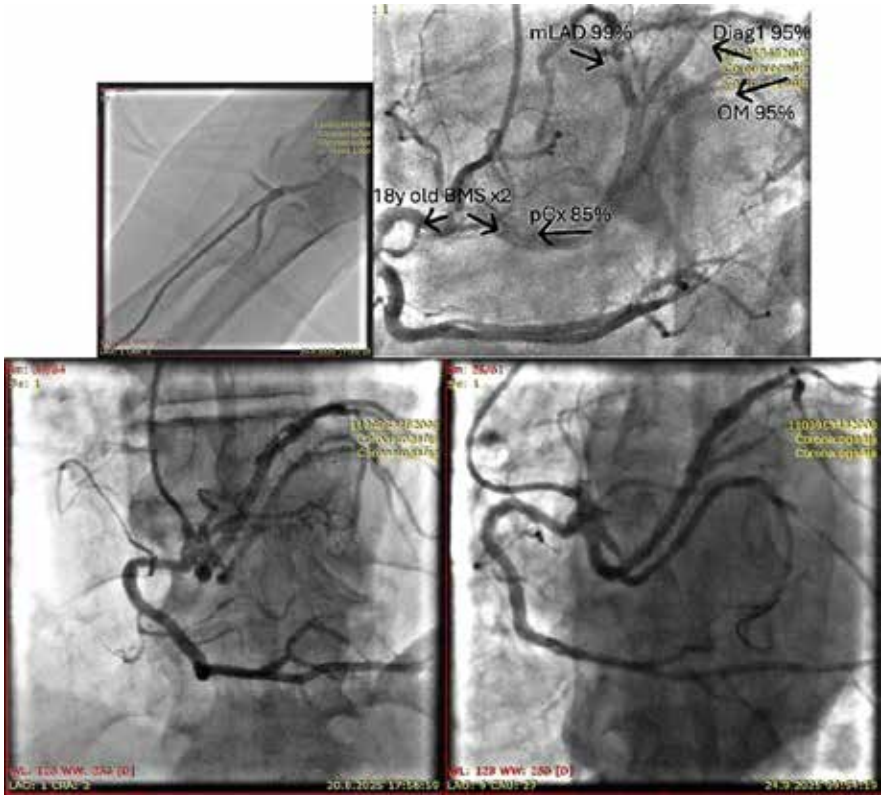


Figure 6. Coronary angiography: we meet the old forgotten friend again

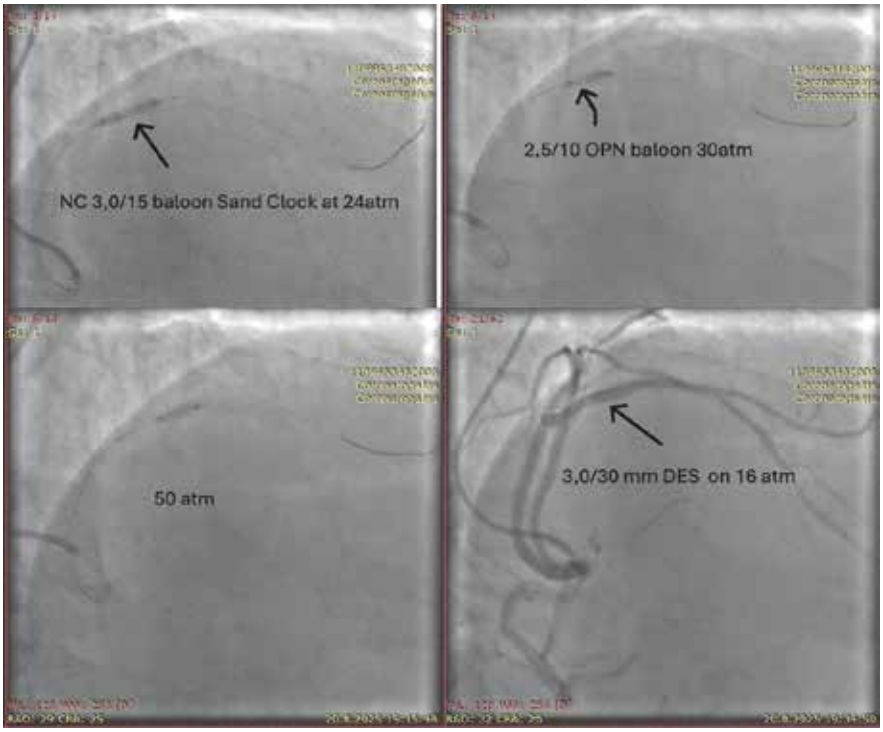


Figure 7. Multiple lesion preparation finally ended with super high pressure balloon inflation

tomical constraints or ostial anomalies may limit the use of atherectomy or intravascular lithotripsy.

4. Staged Multivessel Revascularisation

The combination of DES (LCx) and DEB (OM) reflects a contemporary, individualised PCI strategy. Deferral of the asymptomatic diagonal lesion was appropriate and guideline-consistent[7].

5. Prognostic Considerations in Single Coronary Ostium

Although the patient had a benign retro-aortic course, congenital anomalies require lifelong clinical surveillance, as progression of native disease—not congenital anatomy—may become the dominant risk over time.

Figure 8. PCI No3 Procedure (one month after using the 50 atm balloon)

Conclusion

This case illustrates the convergence of congenital coronary anatomy, long-term stent behaviour, and modern interventional management of heavily calcified lesions. Despite rare anatomy, high-pressure lesion preparation, careful procedural planning, and staged PCI resulted in excellent outcomes. Lifelong follow-up remains essential in patients with a single coronary ostium, even when initial stent results appear durable.

References

1. Angelini P. Coronary artery anomalies—current clinical issues: definitions, classification, incidence, clinical relevance, and treatment guidelines. Tex Heart Inst J. 2002;29(4):271–278.
2. Yamanaka O, Hobbs RE. Coronary artery anomalies in 126,595 patients undergoing coronary arteriography. Cath Cardiovasc Diagn. 1990; 21(1):28-40.
3. Gräni C, Buechel RR, Kaufmann PA, et al. Coronary artery anomalies: prevalence, pathophysiology, and clinical relevance. Eur Heart J. 2017;38:143–150.
4. Darki A, Motiwala A, Bakhos L, et al. Technical success and long-term outcomes after anomalous right coronary artery stenting with cardiac computed tomography angiography correlation. Catheter Cardiovasc Interv 2020; 96(2):320-327
5. C.J. Koppel, Vliegen HW, Bokenkamp R, et al. Leiden Convention coronary coding system European Heart Journal - Cardiovascular Imaging 2022; 23:412–422
6. Barbato E, Shlofmitz E, Milkas A, et al. State-of-the-art: evolving technologies for coronary lesion preparation. Eur Heart J. 2021;42:269–283.
7. Neumann F-J, Sousa-Uva M, Ahlsson A, et al. ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J 2018; 39: 87–165.
8. Byrne RA, Rossello X, Coughlan JJ, et al. 2023 ESC/EACTS Guidelines for the management of chronic coronary syndromes. Eur Heart J 2023; 44(38): 3720-3826.

Sažetak

Ponovljena perkutana koronarna intervencija kod pacijenta sa jedinim koronarnim otstupom iz desnog koronarnog sinusa: 18-godišnji klinički tok

Oliver Kalpak[1], Nikola Manev[1], Aleksandar Jovkovski[1], Antonio Georgiev[1], Hristo Pejkov[1]
[1]University Clinic for Cardiology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, RN Macedonia

Ovaj rad opisuje 18-godišnji produženi klinički tok pacijenta sa retkim jedinim koronarnim otstupom iz desnog koronarnog sinusa. Pacijent je podvrgnut perkutanoj koronarnoj intervenciji (PCI) sa stentovima bez leka (BMS) u proksimalnom segmentu leve prednje silazne arterije (pLAD) i proksimalnom segmentu desne koronarne arterije (pRCA) 2007. godine, sa kasnijom dugoročnom prohodnošću i bez restenoze implantiranog stenta skoro dve decenije. U avgustu 2025. godine, pacijent se klinički prezentuje sa akutnim koronarnim sindromom bez elevacije ST segmenta (NSTEMI-ACS) izazvanom novom, jako kalcifikovanom stenozom medijalnog segmenta LAD od 99%. PCI je zahtevala tretiranje plaka primenom balona sa visokim pritiskom (OPN balona super visokog pritiska do 50 atm), nakon čega je usledila implantacija stenta sa lekom (DES) uz odličan angiografski rezultat. Nakon mesec dana, sprovedena je elektivna perkutana koronarna intervencija (PCI) koja je rešila tešku stenozu na proksimalnom segmentu cirkumfleksne arterije (pLCx) i suokluzivnu leziju marginalne grane (OM), primenom DES-a i balonom obloženim lekom (DEB).
Ovaj slučaj ističe prirodni tok koronarne ateroskleroze kod kongenitalnih koronarnih anomalija, dugoročnu trajnost BMS rane generacije i tehničke izazove koje predstavlja ekstremna kalcifikacija. On naglašava važnost doživotnog praćenja i prilagođavanja strategije revaskularizacije kod pacijenata sa anatomijom jednog odstupa koronarne arterije.

Ključne reči: *urođene anomalije koronarnih arterija, perkutana koronarna intervencija, balon sa super visokim pritiskom, stent sa oslobađanjem leka*

Srce i krvni sudovi 2025; 44(4): 133-135

Case report

Transcatheter Aortic Valve Implantation in Large and Extra-Large Aortic Annuli: Contemporary Evidence and Performance of Third-Generation Devices

Igor Ivanov[1,2], Igor Tomas[1], Milenko Čanković[1,2]

[1]Institute for Cardiovascular Diseases of Vojvodina, Sremska Kamenica, Serbia, [2]Novi Sad Medical Faculty, University of Novi Sad, Novi Sad, Serbia,

Abstract

Background: Large and extra-large (XL) aortic annuli represent one of the most challenging anatomical subsets in contemporary transcatheter aortic valve implantation (TAVI), owing to dimensions exceeding Instructions for Use (IFU) limits, elliptical annular geometry, and heavy calcification. Recent expansion of device sizes and refinement of sealing systems in third-generation valves have enabled TAVI in anatomies previously considered borderline or unsuitable.

Methods: This narrative review summarizes anatomical definitions, procedural outcomes, and hemodynamic performance of four major third-generation platforms—Evolut 34 mm, SAPIEN 3 29 mm, Navitor TITAN 35 mm, and Myval XL—based on multicenter registries and dedicated large-annulus cohorts.

Results: Large annulus is typically defined as 500–683 mm², while XL annulus corresponds to >683 mm² or perimeter >94 mm. Across major databases procedural success ranged from 94–98%, with 30-day mortality 1–3% and stable hemodynamics despite annular dimensions beyond standard IFU ranges. Paravalvular leak (PVL) remains the primary challenge; however, modern sealing technologies (NaviSeal™, PET cuff, pericardial wrap) significantly mitigate this risk.

Conclusion: Contemporary evidence shows that TAVI in large and XL annuli is feasible, safe, and associated with excellent early outcomes when supported by precise CT-guided planning and appropriate device selection. Future prospective comparative studies are warranted to refine device-specific indications and long-term durability in this anatomically demanding population.

Key-words Aortic stenosis, TAVI, large annulus, extra-large annulus, SAPIEN 3, Evolut 34, Navitor TITAN, Myval XL

Introduction

Transcatheter aortic valve implantation (TAVI) has transformed the treatment of severe aortic stenosis. However, patients with large and particularly extra-large (XL) aortic annuli remain among the most demanding subsets in contemporary practice. Annular dimensions that exceed manufacturer-recommended ranges (Instructions for Use, IFU), combined with elliptical geometry and increased calcific rigidity, can impair coaxial deployment, expansion, and sealing of the prosthetic valve. The development of third-generation devices and the availability of large-size prostheses—Evolut 34 mm, SAPIEN 3 29 mm, Navitor TITAN 35 mm, and Myval XL (30.5/32 mm)—have expanded procedural feasibility in anatomies that historically required surgery or were considered borderline for TAVI.

Large aortic annulus is typically defined as an area of 500–683 mm², while extra-large annulus corresponds to an area >683 mm² or a perimeter >94 mm. These thresholds are widely used in contemporary CT-based studies and registries evaluating TAVI performance in challenging anatomies.

Evidence from Large-Annulus Registries

One of the most influential sources for understanding this population is the **TAVR-LARGE registry**, a multicenter analysis including 833 patients treated with third-generation platforms—primarily the balloon-expandable (BEV) SAPIEN 3 (29 mm) and the self-expanding (SEV) Evolut R (34 mm)[1]. A dedicated subgroup of 124 patients presented with XL annuli (mean area ≈704 mm²), enabling evaluation of procedural feasibility beyond standard IFU limits. The registry demonstrated a high overall procedural success of approximately 94%, a 30-day mortality of 2.4%, and a 1-year mortality of 9%. Hemodynamic performance was stable in both platforms, while moderate-to-severe paravalvular leak (PVL) occurred in only 3–5% of patients. Differences between BEV and SEV were consistent with expected device-class behavior: BEV systems were associated with lower PVL and lower pacemaker implantations, while SEV systems provided larger effective orifice areas and lower gradients.

The **German Aortic Valve Registry (GARY)** further supported these findings. In more than 5,000 patients with annular diameters ≥26 mm, early clinical outcomes (30-

Corresponding author: Prof Igor Ivanov, MD,PhD, e-mail: ivanovigor05@gmail.com

day mortality 2–3%) were comparable to standard-annulus populations, with preserved hemodynamics and predictable differences between BEV and SEV platforms[2].

A significant contribution to understanding extreme anatomies comes from the prospective cohort of **Hof et al.**, which included 144 patients with annulus area >683 mm² [3]. These anatomies frequently presented with pronounced ellipticity and extensive calcification. Despite these challenges, technical success was high (≈96%), overall implantation success reached 82–85%, and 30-day mortality remained low (2–3%). Moderate PVL occurred slightly more frequently than in standard-annulus controls but without adverse impact on early clinical outcomes. The authors concluded that TAVI in extreme annular dimensions remains feasible and clinically safe when supported by meticulous CT-based planning and appropriate device selection.

Performance of specific third-generation systems

Self-expanding supra-annular design and a nitinol frame provide large effective orifice areas and low transvalvular gradients—features particularly relevant for large-annulus patients with higher body surface area. Across large-annulus series, implantation success ranged from 93–96%, gradients from 6–10 mmHg, and 30-day mortality from 1–2%[4–5].

The EnVeo PRO delivery system uses an 18 Fr equivalent sheath for the 34-mm model, requiring approximately 7.3 mm minimal femoral lumen, with vascular complications of 4–6% reported in large-annulus cohorts.

SAPIEN 3 is the best-studied BEV system in large and XL annuli. In annulus areas ranging from 683–850 mm², procedural success approached 97%, 30-day mortality remained around 1%, and moderate PVL occurred in 3–4%[6]. The PET outer skirt contributes substantially to PAR mitigation in elliptical geometries[7]. BEV systems consistently demonstrated the lowest pacemaker rates in comparative analyses[8]. The Commander system uses a 14–16 Fr sheath and requires a minimum femoral lumen of 5.5–6.0 mm.

Navitor and Navitor TITAN incorporate an intra-annular design and the adaptive NaviSeal™ cuff, which improves sealing in irregular or elliptical annuli. Early registries report technical success of 95–98%, gradients of 7–10 mmHg, and moderate PVL in only ~2–3%[9-10]. The 35-mm TITAN model is clinically important as it covers annular diameters of 27–30 mm, filling a previously underserved anatomical range. Unlike other large SEV prostheses, TITAN uses a 15 Fr equivalent introducer, with a minimal femoral lumen requirement of ≈5.5 mm, making it one of the lowest-profile solutions in its class.

Myval XL is the only BEV platform designed specifically for extremely large annuli, covering areas up to ≈840 mm². The MyVal-1 and subsequent multicenter analyses demonstrate implantation success >95%, moderate PVL 0–3%, and gradients 7–12 mmHg[11]. The Navigator system uses a 14 Fr Python introducer for standard sizes and 16–18 Fr for XL models, with estimated minimal femoral lumen of 5.5–6.0 mm.

Conclusion

Available evidence demonstrates that large and extra-large aortic annuli, despite anatomical complexity and elevated risks of incomplete expansion and paravalvular regurgitation, are increasingly well managed in contemporary TAVI practice. The largest registries consistently confirm high technical success (94–98%), low early mortality (1–3%), and stable hemodynamics even beyond standard IFU limits.

Modern sealing technologies and the development of large-size devices—Evolut 34 mm, SAPIEN 3 29 mm, Navitor TITAN 35 mm, and Myval XL 30.5/32 mm—have expanded therapeutic possibilities, while advances in low-profile delivery systems improved procedural safety and broadened transfemoral access feasibility.

Future prospective comparative studies will be essential for refining optimal prosthesis selection and evaluating long-term durability in this anatomically demanding population.

References

1. Armijo G, Tang GHL, Kooistra N, et al. Third-generation balloon and self-expandable valves for aortic stenosis in large and extra-large annuli: The TAVR-LARGE registry. *Circ Cardiovasc Interv.* 2020. doi: 10.1161/CIRCINTERVENTIONS.120.009047
2. Piayda K, Bauer T, Beckmann A, et al. Procedural results in patients undergoing TAVI with aortic annuli ≥26 mm: Insights from the German Aortic Valve Registry. *Am J Cardiol.* 2022; 164:111–117
3. Hof A, Wienemann H, Veulemans V, et al. Feasibility and outcomes of third-generation TAVI in patients with extra-large annulus. *Clin Res Cardiol.* 2024; 113:107–115
4. Gallo F, Gallone G, Kim W-K, et al. Procedural outcomes of the 34 mm EvolutR Transcatheter valve in a real-world population insights from the HORSE multicenter collaborative registry. *Int J Cardiol* 2022; 361:55-60.
5. Abdelghani M, Mankerious N, Allali A, et al. Valve performance after TAVI in large vs. small annuli. *JACC Cardiovasc Interv.* 2018; 11:2507–2518.
6. Miyasaka M., Yoon S.H., Sharma R.P., et al. Clinical outcomes of transcatheter aortic valve implantation in patients with extremely large annulus and SAPIEN 3 dimensions based on post-procedural computed tomography. Circ J. 2019; 83:672–680.
7. Tang GHL, Zaid S, George I, et al. Aortic root geometry and paravalvular leak with SAPIEN 3. *JACC Cardiovasc Interv.* 2018; 11:1377–1387.
8. Aoun J, Zaid S, Goel S, Reardon MJ. A Comprehensive Evaluation of the NAVITOR Transcatheter Aortic Valve Replacement System. Heart Int 2024;18(1):26–29.
9. Worthley SG, Giordano A, Corcione N, et al. 30-Day and 1-Year Outcomes of Navitor Transcatheter Aortic Valve in Low- or Intermediate-Risk Patients. *JACC Cardiovasc Interv.* 2025 18(20):2517-27.
10. Sharma SK, Rao RS, Chandra P, et al. First-in-human evaluation of the Myval THV. *EuroIntervention.* 2020; 16(5):421-429
11. Holzamer A, Bedogni F, van Wyk P, et al. Performance of the 32-mm Myval THV in extremely large annuli: First global multicenter experience. *Catheter Cardiovasc Interv.* 2023; 102(7):1364-75.

Sažetak

Transkateterska zamena aortnog zaliska kod pacijenata sa velikim i veoma velikim aortnim anulusom: Savremeni dokazi i performanse zalistaka treće generacije

Igor Ivanov[1], Igor Tomas[2], Milenko Čanković[1]

[1]Medicinski fakultet Univerziteta u Novom Sadu, Srbija, [2]Institut za kardiovaskularne bolesti Vojvodine, Sremska Kamenica, Srbija

Uvod i Cilj: Veliki i ekstra veliki (XL) aortni anulusi predstavljaju jednu od najzahtevnijih anatomskih podgrupa u savremenoj transkateterskoj implantaciji aortnog zalistka (TAVI), zbog dimenzija koje prelaze ograničenja uputstva za upotrebu (IFU), postojeće eliptične geometrije anulusa i izraženih kalcifikacija. Nedavno proširenje veličine zalistaka i usavršavanje sistema zaptivanja u platformama treće generacije omogućili su TAVI i u anatomijama koje su se ranije smatrale graničnim ili neprikladnim.

Metode: Ovaj narativni pregled sumira anatomske definicije, proceduralne ishode i hemodinamske performanse četiri glavne platforme treće generacije - Evolut 34 mm, SAPIEN 3 29 mm, Navitor TITAN 35 mm i Myval XL - na osnovu multicentričnih registara i namenskih kohorti kod pacijenata sa velikom dimenzijom anulusa.

Rezultati: Veliki anulus se tipično definiše kao 500–683 mm², dok XL anulus odgovara >683 mm² ili perimetru >94 mm. U velikim bazama podataka uspeh procedura se kretao od 94–98%, sa mortalitetom u roku od 30 dana od 1–3% i stabilnom hemodinamikom uprkos dimenzijama anulusa izvan standardnih IFU raspona. Paravalvularno curenje (PVL) ostaje primarni izazov; međutim, moderne tehnologije zaptivanja (NaviSeal™, PET manžetna, perikardijalni omot) značajno umanjuju ovaj rizik.

Zaključak: Savremeni dokazi pokazuju da je TAVI kod velikih i XL anulusa izvodljiva i bezbedna metoda koja je povezana sa odličnim ranim ishodima kada je podržana preciznim CT vođenim planiranjem i odgovarajućom platoformom. Buduće prospektivne uporedne studije su potrebne kako bi se precizirale indikacije specifične za platformu i ispitala dugoročna trajnost kod ove anatomski zahtevne populacije.

Ključne reči: *aortna stenoza, TAVI, veliki anulus, SAPIEN 3, Evolut 34, Navitor TITAN, Myval XL*

11. ZAJEČARSKI SIMPOZIJUM INTERVENTNE KARDIOLOGIJE

Generalni sponzor

APTUS

Zlatni sponzor

VICOR

Srebrni sponzori

MAGNA PHARMACIA

HERMES PHARMA

Medtronic

Sponzori kongresa

Soul Medical

MEDICA LINEA PHARM

Abbott

Boehringer Ingelheim

KRKA

AstraZeneca

CIS Medical d.o.o.

Hemofarm STADA GRUPA

Amicus SRB

novo nordisk®

MEGAPHARM

Galenika

mark medical™ empowering healthcare.

ADOC

Goodwill

Medijski partneri kongresa

pixArt web&graphics studio

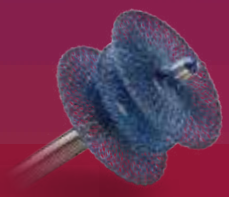
za media

103 FM MAGNUM RADIO

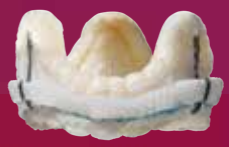
Abbott

STRUCTURAL HEART

FOR EVERY GENERATION OF LIFE



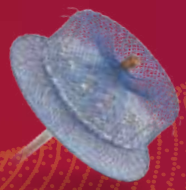
Amplatzer Piccolo™ Occluder



Epic™ Supra Aortic Stented Tissue Valve

Regent™ Mechanical Heart Valve

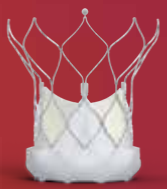
Epic™ Mitral Stented Tissue Valve



Amplatzer™ Amulet™ Left Atrial Appendage Occluder

MitraClip™ Transcatheter Edge-to-Edge Repair

TriClip™ Transcatheter Edge-to-Edge Repair



Navitor™ Transcatheter Aortic Valve Implantation System

Tendyne™ Transcatheter Mitral Valve Replacement System

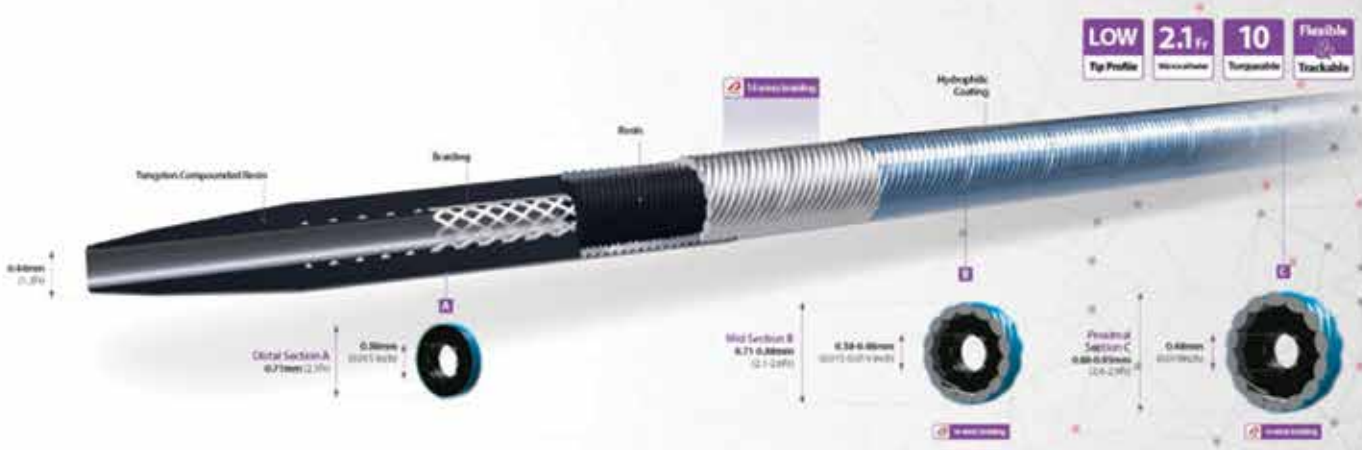
CAUTION: This product is intended for use by or under the direction of a physician. Prior to use, reference the Instructions for Use, inside the product carton (when available) or a eifu.abbottvascular.com or at medical.abbott/manuals for more detailed information on Indications, Contraindications, Warnings, Precautions and Adverse Events. Information contained herein for **DISTRIBUTION in Europe, Middle East and Africa ONLY**. Always check the regulatory status of the device in your region. Photo(s) on file at Abbott.

Abbott Vascular International BVBA
Culliganlaan 2B, 1831 Diegem, Belgium

www.cardiovascular.abbott

Your dreams. Woven together.

ASAHI INTECC



ASAHI Corsair Pro XS

Microcatheter

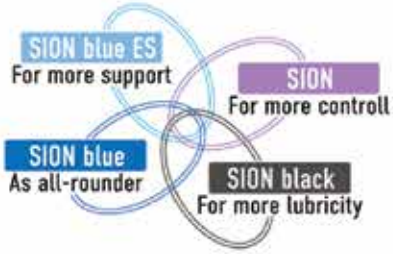
ASAHI SION blue ES

PTCA GUIDE WIRE

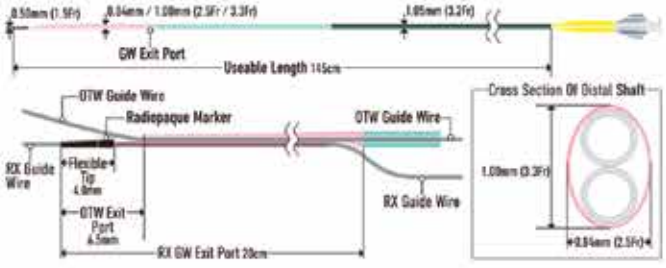
Supportive frontline guide wire

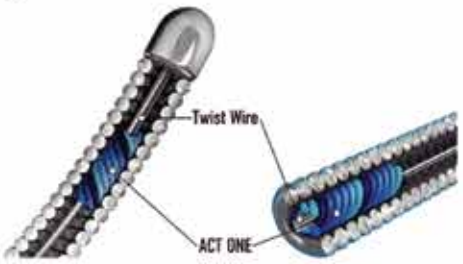
ASAHI SASUKE

Stability – Real Value in Your Procedure



Distal shaft cross section





APTUS ®

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

SR_BCM-01-2023_V1_printreminder
Datum odobrenja: 07.10.2023.

Vivid™ E95

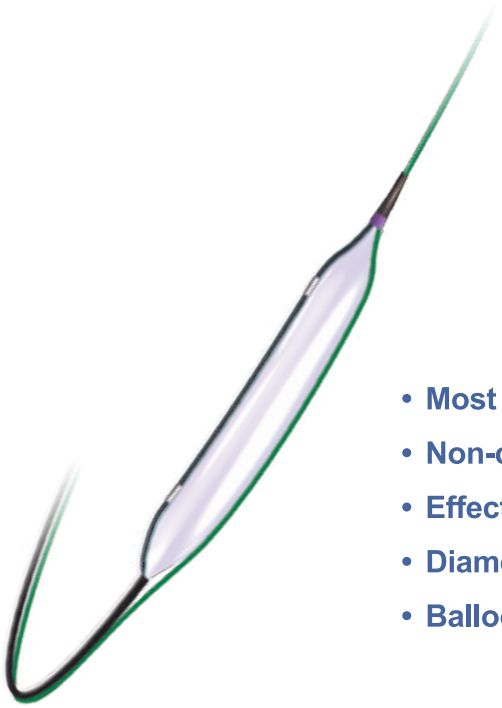
ULTRA EDITION

GE HealthCare

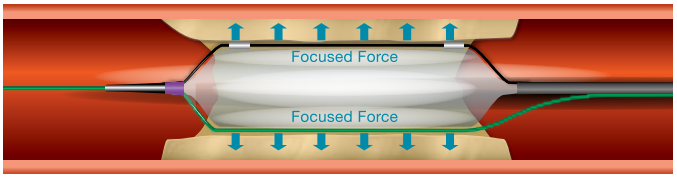
MAGNA PHARMACIA

scoreflex® NC

Coronary Dilatation Catheter



Focused Force Angioplasty for Non-Compliant Lesion Preparation



- Most competitive crossing profile
- Non-compliant safety
- Effective plaque modification
- Diameter range 1.75 mm to 4.0 mm with quarter sizes available
- Balloon lengths 10 mm to 20 mm

OrbusNeich®

Pioneers in life-changing technologies

SANOmed

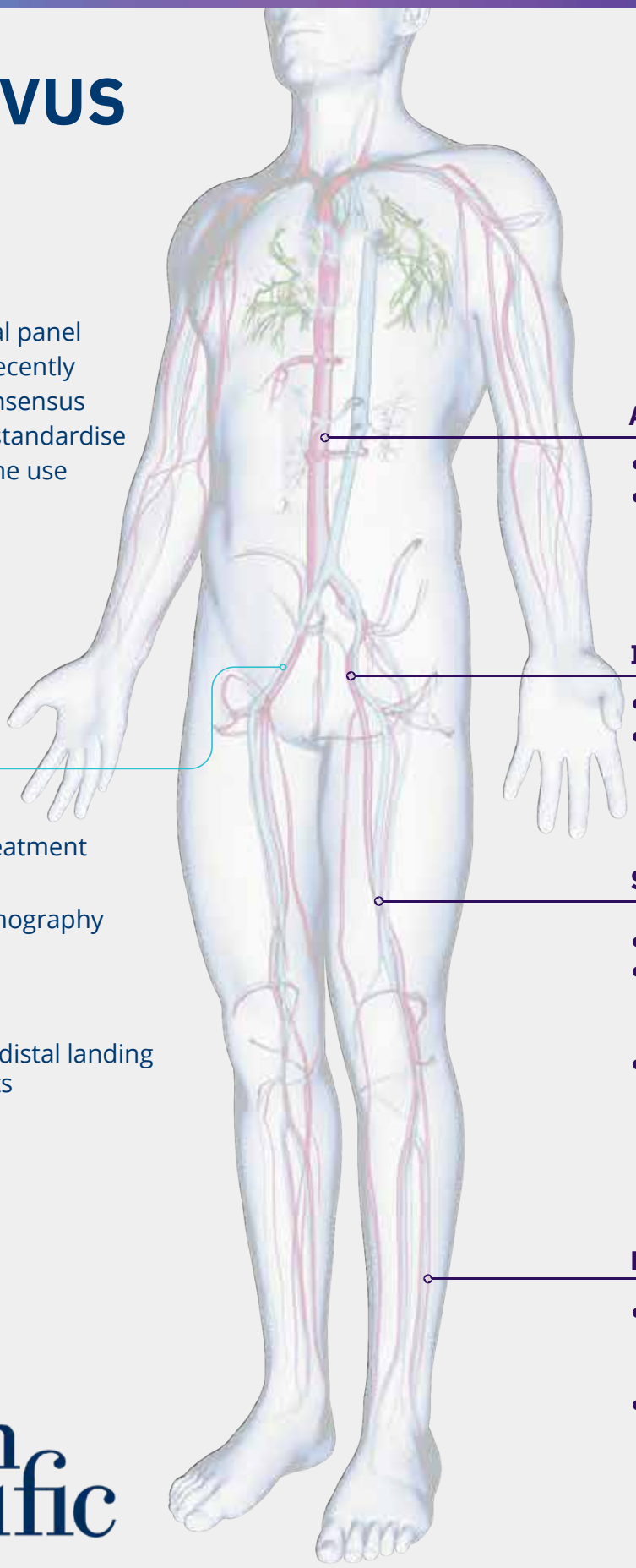
SANOmed

Vojislava Ilića 69,
11054 Beograd
Tel/fax: 011/40 80 083
office@sanomed.rs

PHILIPS OLYMPUS SynCardia SYSTEMS, LLC
Occlutech TransMedics BAYER
Johnson&Johnson Boston Scientific CHECKPOINT CARDIO

Why We IVUS

An international panel of 40 experts recently established consensus to encourage, standardise and optimise the use of IVUS.8



Aortic

- Reduced endo leaks
- Improved sizing accuracy

Iliac

- Improved outcomes
- Reduced adverse events

Deep vein obstruction

- IVUS led to change in treatment plan in 57% cases
- IVUS was superior to venography in delineating:
  - Degree of stenosis
  - Location of stenosis
  - Optimal proximal and distal landing zones for venous stents

SFA

- Reduced amputations
- 4-5x more dissections detected than with angiography
- Improved accuracy in predicting restenosis

BTK

- 4-5x more dissections detected than with angiography
- More accurate RVD than with angiography

BTK: Below the knee
RVD: Reference vessel diameter
SFA: Superficial femoral artery

Boston Scientific

VICOR
+381 11 30 16 492 www.vicor.rs office@vicor.rs Bulevar maršala Tolbuhina 42, Novi Beograd

CORVIVA®
rivaroksaban

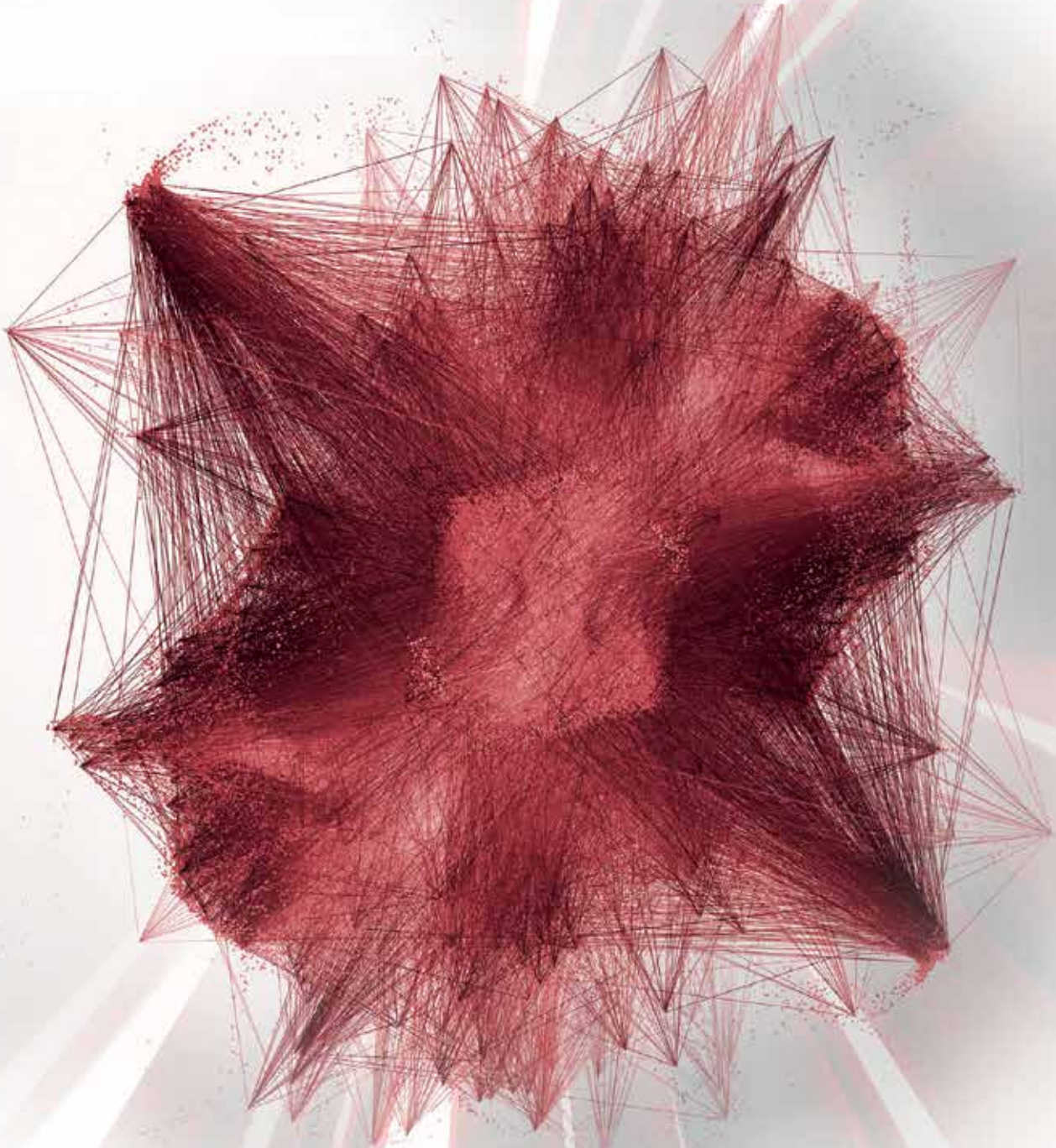
Actavis | teva

Actavis d.o.o.
Đorđa Stanojevića 12, 11070 Novi Beograd
tel. 011/20-99-300; fax 011/20-99-301

SAMO ZA STRUČNU JAVNOST • DATUM KREIRANJA DOKUMENTA: Avgust 2024. • CARD-RS-00174
Upućujemo zdravstvene radnike na poslednji celokupni sažetak karakteristika leka i uputstva za lek Corviva® 10, 15, 20 mg koji su dostupni na internetskoj stranici Agencije za lekove i medicinska sredstva www.alims.gov.rs. Način izdavanja: na recept.

Rufixalo®

rivaroksaban 10,15,20 mg



ALKALOID

Reference: 1. Sažetak karakteristika leka Forxiga, poslednja revizija teksta Mart 2023.
2. Jhund PS et al. Dapagliflozin across the range of ejection fraction in patients with heart faliure: a patient- level, pooled meta analysis of DAPA-HF and DELIVER Nat Med. 2022. Sep; 28(9):1956-1964
3. Wheeler DC et al. The dapagliflozin and prevention of adverse outcomes in chronic kidney disease (DAPA-CKD) trial: baseline characteristics; Nephrol Dial Transplant. 2020; 35(10)1700–1711.

RRR - relativna redukcija rizika; **ARR** - apsolutna redukcija rizika; **KV** - kardiovaskularni; **LVEF** - ejekciona frakcija leve komore; **HBB** - hronična bolest bubrega

Broj rešenja ALIMS odobrenja: 000002625 2024 59010 006 000515 069 04 004 od 29.05.2024.

Pre propisivanja leka Forxiga®, molimo pročitajte poslednji odobreni sažetak karakteristika leka, Forxiga® mart 2023.

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

SAMO ZA STRUČNU JAVNOST
RS-6167, oktobar 2024.

8 Galenika

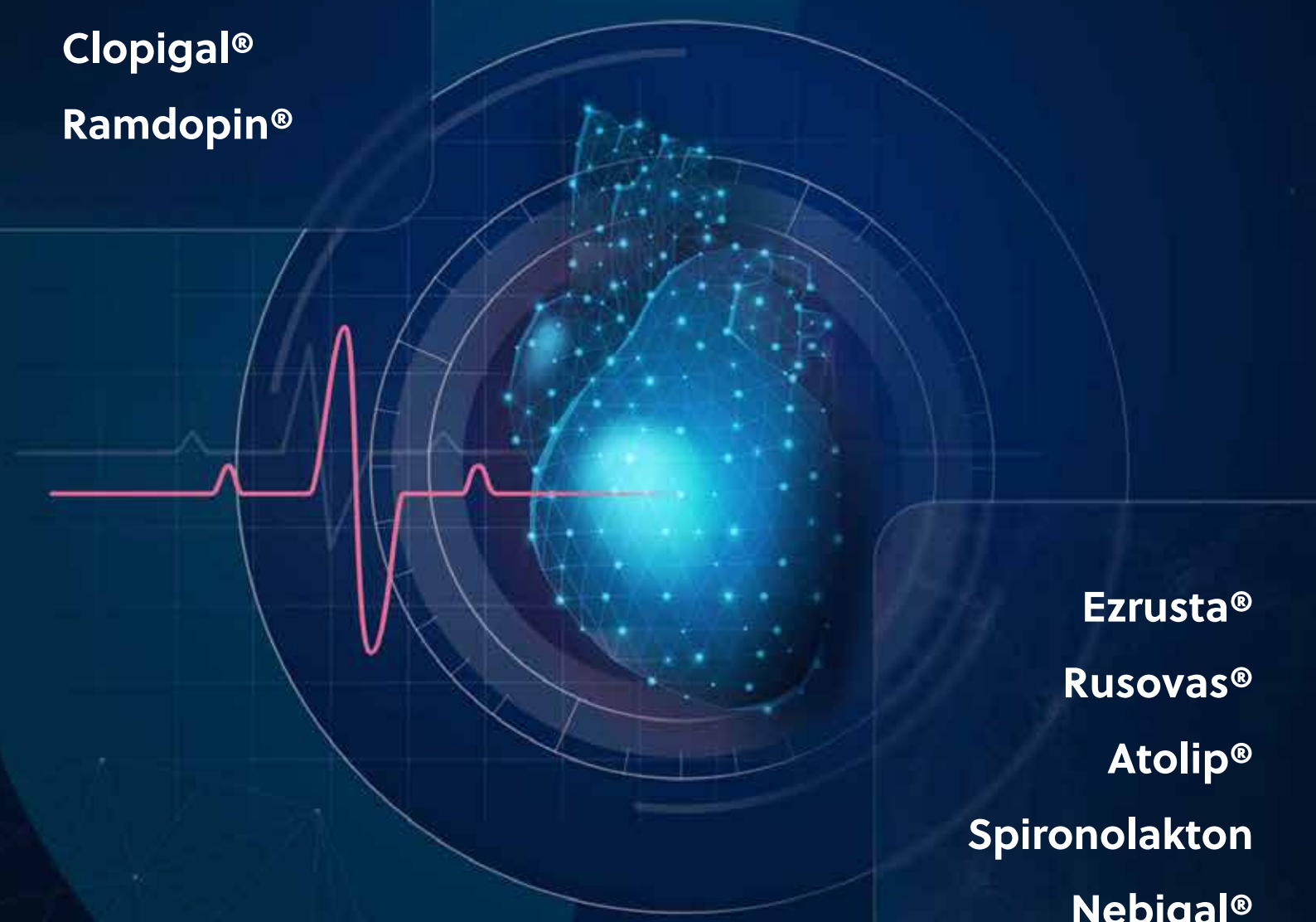
Rivarox®

Galipeks®

Gartyz®

Clopigal®

Ramdopin®



Ezrusta®

Rusovas®

Atolip®

Spironolakton

Nebigal®

Bisprol®

Kardiologija Galenika

DUOPRESINN®

film tablete, 30 x 20 mg/5 mg
film tablete, 30 x 40 mg/5 mg
film tablete, 30 x 40 mg/10 mg
INN: olmesartan medoksomil, amlodipin

Sinergija u jednom koraku

Lek se izdaje uz lekarski recept
Samo za stručnu javnost

INNventa
Inventive Pharma Solutions

Nosilac dozvole za lek:
INNVENTA PHARM D.O.O. Republika Srbija

ROXERA PLUS®

rosuvastatin/ezetimib

10 mg/10 mg

20 mg/10 mg

40 mg/10 mg

KRKA

Pre upotrebe detaljno proučiti uputstvo! O indikacijama, merama opreza i neželjenim reakcijama na lek, posavetujte se sa lekarom ili farmaceutom.

LEQVIO®▼ (inklisiran) može da obezbedi dugotrajnu kontrolu LDL holesterola vaših pacijenata[1,2]

*Dve doze godišnje nakon dve početne doze.[1]

Bezbednost i efikasnost inklisirana kod dece mlađe od 18 godina još nije utvrđena.

LEQVIO®
inklisiran

Na kraju otvorenog produženog ispitivanja ORION-8,

Skoro 80% pacijenata je postiglo svoj ciljni LDL-h i održalo ga dugoročno[3]

Predefinisani ciljevi lipida: ASCVD <1,8 mmol/L (<70 mg/dL); Ekvivalent rizika od ASCVD <2,6 mmol/L (<100 mg/dL)

Bezbednost i efikasnost inklisirana kod dece mlađe od 18 godina još nije utvrđena.

Reference: 1. LEQVIO sažetak karakteristika leka, datum revizije mart 2023. **2.** Ray KK, Wright RS, Kallend D, et al; ORION-10 and ORION-11 Investigators. Dva ispitivanja faze 3 inklisirana kod pacijenata sa povišenim LDL holesterolom. N Engl J Med. 2020;382(16):1507-1519. **3.** Wright RS, Raal FJ, Koenig W, et al. ORION-8: dugoročna efikasnost i bezbednost dva puta godišnje kod pacijenata sa visokim kardiovaskularnim rizikom. Podaci predstavljeni na: European Society of Cardiology Congress; August 28, 2023; Amsterdam, Netherlands.

INDIKACIJE Lek Leqvio je indikovan za primenu kod odraslih sa primarnom hiperholesterolemijom (heterozigotnom familijarnom i nefamilijarnom) ili mešanom dislipidemijom, kao dodatak dijeti u kombinaciji sa statinom ili zajedno sa statinom i drugim terapijama za snižavanje vrednosti lipida kod pacijenata koji ne mogu da postignu ciljne vrednosti LDL-holesterola uz primenu najveće podnošljive doze statina, ili sam ili u kombinaciji sa drugom terapijom za snižavanje vrednosti lipida kod pacijenata koji ne podnose statine, ili kod kojih je lečenje statinima kontraindikovano.

Samo za stručnu javnost.

▼Ovaj lek je pod dodatnim praćenjem. Time se omogućava brzo otkrivanje novih bezbednosnih informacija. Zdravstveni radnici treba da prijave svaku sumnju na neželjene reakcije na ovaj lek. Za način prijavljivanja neželjenih reakcija videti odeljak 4.8.

Režim izdavanja leka: Lek se može upotrebljavati u stacionarnoj zdravstvenoj ustanovi, izuzetno lek se može izdavati i uz recept, u cilju nastavka terapije kod kuće, što mora biti naznačeno i overeno na poleđini recepta.

Broj i datum rešenja Leqvio, 284mg, rastvor za injekciju u napunjenom injekcionom špricu: 515-01-02095-21-001 od 30.06.2023.

Datum revizije sažetka karakteristika leka: 24.03.2023.

Upotreba materijala odobrena od ALIMS-a, broj rešenja: 000049407 2025 59010 006 000 515 069 04 002 od 03.04.2025. godine

NOVARTIS

Predstavništvo Novartis Pharma Services Inc.
Omladinskih brigada 90a, 11070 Novi Beograd, Srbija
tel. +381 11 2014000

RS_05 25_FA-11437255

JEDNOM NEDELJNO

wegovy®

semaglutid 2,4 mg