UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA

SRCE I KRVNI SUDOVI

Volumen 33 Broj 1 2014. godina

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

* Data pismena saglasnost za članstvo u odborima. Uredništvo ostaje otvoreno za sve promene i dopune uređivačkih odbora.

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 elektronskom putem na adresu: srceikrvnisudovi.urednistvo@gmail.com i branko.beleslin@gmail.com, naslovljeno na: prof. dr Miodrag Ostojić, 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 prelazi 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 bude 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 abstrakta 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. Fotografiju moraju da budu u tif, eps ili ai formati, 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 pošalje recenzentima i vrati autorima.

INSTRUCTIONS FOR AUTHORS

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

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

The manuscript with all appendices should be addressed to:
Prof. Miodrag Ostojic, MD, PhD
Editor-in-Chief, Heart and Blood Vessels
and mailed to srceikrvnisudovi.urednistvo@gmail.com, branko.beleslin@gmail.com and mostojic2003@yahoo.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.

UDRUŽENJE KARDIOLOGA SRBIJE
CARDIOLOGY SOCIETY OF SERBIA

SRCE I KRVNI SUDOVI

Volumen 33 Broj 1 2014. godina

Sadržaj

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 Miodrag Ostojić, Godina 4,
Volumen 33, Broj 1
Beograd, Koste Todorović 8: Udruženje kardiologa Srbije
2014-Beorad: Newassist doo
Tromesečno-Broj 1 izašao 2011. god.

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

Srce i krvni sudovi 2014; 33(1): 1-7

Specijalan rad

The coronary stent story

Leo Finci, MD, MSc, PhD, FMH, FESC, FACC.

Cardiology Institut Champel, Geneva

Abstract The objective of this article is to narrate the story of stent development as witnessed by the author who was present from the very beginning. By the end of eighties, coronary angioplasty (PTCA) had clearly shown its limitations such as abrupt vessel occlusion, dissection and restenosis rate of up to 35%. The Medinvent Company developed a self-expanding-stent that was implanted in a first series of patients by Ulrich Sigwart in Lausanne, Switzerland in 1986. However, the multicenter study in 1989 had disastrous results, with 25% of stent occlusion rate and restenosis of >20% in remained patients. The Palmaz-Schatz stent was first bare-metal stent (BMS) largely used in the world since 1990. The heavy anticoagulation treatment was abolished by A. Colombo in 1993. By 1997, about 17 new models existed, still the abrupt stent occlusion, subacute stent thrombosis (2-4%), and restenosis (25-30%), were major problems. Drug-eluting stents (DES) were developed to specifically address the problems of restenosis encountered with BMS. The sirolimus eluting stents used since 2002 have shown better clinical results than paclitaxel eluting stents arriving in 2004, but newcomers using zotaralimus, everolimus and biolimus elusions have arrived showing even better results. Currently, the last generation of stent need only 3 months of dual antiplatelet treatment, bioapsorbale coating is only on ab-luminal side of stent, struts are thin and metallic cage is laser cut hypotube. The case of chronic total coronary occlusion is discussed, as this indication benefited most from the stent development. Bioresorbable vascular scaffolds (BVS) are intended to overcome most drawbacks of stents: the presence of a metallic cage, positive remodelling, and normal vasomotor vessel function, but long-term results are still unknown.

Key words stent, coronary, history, bare metal stent, drug elution, chronic total coronary occlusion, bioresorbable vascular scaffolds

„Once upon a time there was a coronary device, named «stent»[1]. Its name comes from a dentist[2], and a noble German prince coming from the battle-field of restenosis and residing Swiss castle help him to become a stronghold of human coronary vessels[3,4] . Indeed, the stent story is so close to a tale! Since its first clinical use, with several generations of stents, throughout years of enthusiasm, complications and drawbacks[5,6], stents successfully improved to new scaffolds. The objective of this article is not to scientifically analyze all the phases of stent development, its clinical application and studies; it is rather to narrate the story as witnessed by a man who has been present from the very beginning.

Pre-stent era

By the end of eighties, coronary angioplasty (PTCA) had clearly showed the limitations (Figure 1). Primary success was relatively acceptable, but there were many drawbacks, such as abrupt vessel occlusion or dissection. In particular the long-term results were limited by the recurrence[7,8]. Many European centres have addressed the question of restenosis after PTCA, as we did in Geneva[9] mainly by new drug treatments using different medications, starting with angiogenesis enzyme inhibitors to steroids, but also using technologies such as lasers or atherectomy. I can still remember a patient

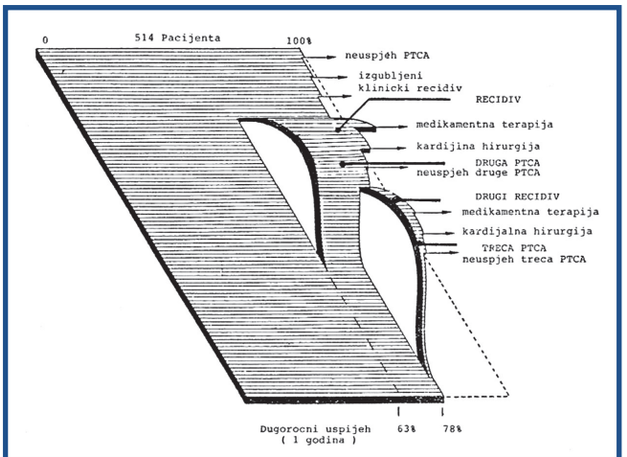


Figure 1. Follow-up of 500 patients after coronary angioplasty (PTCA) - in 1986. Note primary success of only 63% at one year that reaches 78% after repeat procedures.

Correspondence to Leo Finci, Cardiology Institut Champel, Rue Marignac 13, 1206 Geneva, Switzerland, Phone +41 22 792 80 80, Fax +41 22 792 80 81

Figure 2a. Professor Ulrich Sigwart and Dr Finci discussing stent options, Lausanne 1985.

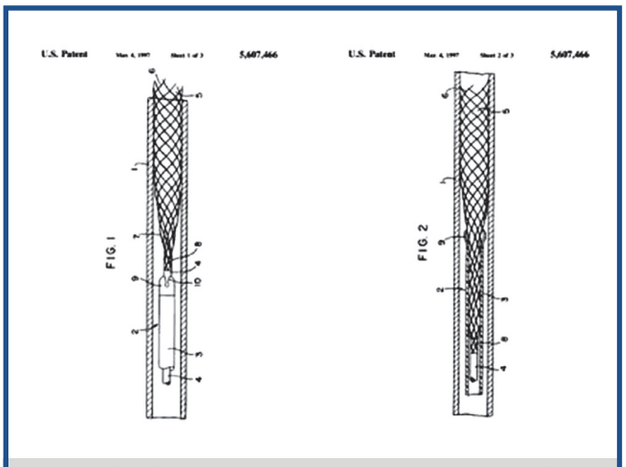


Figure 2b. The Medinvet stent. Acquired by Schneider Medintag AG in 1988, patented in the USA.

that undertook 11 repeated PTCAs for a proximal LAD lesion, sometimes restenosed, but mainly caused to balloon injury around the lesion.

Early stents

The Medinvent company located in canton de Vaud, in French Swiss part, was involved with many new technologies, such as artificial skin. With Prof. Rutisahuser, from Geneva University Hospital, we were invited to discuss the stent experience in 1985 – we had a hall out of a problem to find location of the company installed in Swiss mountains, in the middle of the cows! In spite the work that had already been done by Medinvent, the decision was made to continue doing only animal study in Geneva before any human experience could be started. It is only that Ulrich Sigwart, of Lausanne University Hospital who had courage to go on! (Figure 2, A and B). One must admit that it was not an easy task at all. Just to make it more clear to understand: the unit of Experimental Surgery, in Lausanne disposed of non-optimal x-ray equipment, so some of the experimental dogs (to start the experience) had to be stented in a human catheterisation laboratory after regular working hour's (Dr Mirkovitch, experimental surgeon in charge at the time-personal communication).

However, during 1986 total of 19 patients were treated by stent implantation mainly for restenosis after PTCA and acute closure, with 3 complications due to stent thrombosis[10]. The first human implantation was successfully done by Puel in Toulouse early that year in acute setting in a case of abrupt closure. During the first live stent summit in Lausanne in 1987, the audience could also witness the first stent thrombosis – while most of the participants enjoyed their lunch, Sigwart kept so busy in the Cathlab.

In the years that followed, the Wallstent was being used in several European centres, including Rotterdam, London and Geneva (Figure 3) but with disastrous result: from about 100 patients that were treated, stent occlusion occurred in 25 patients, and restenosis in 14 other patients[1, 11].

The new stent player came from across the Ocean-USA. Richard Schatz had carefully planned and went on

Figure 3. Prof. Rutishauser, Dr B. Meier et Dr Finci, exploring new PCI material in Geneva University Hospital in 1986

doing studies with a balloon expandable model of an articulated stent[12,13], available at that time in Europe for clinical use, but not in the USA. Colombo implanted successfully first few stents in 1990, Schatz being present with him in Milan that morning; it happened that Schatz was obliged to leave Milan in the afternoon of the same day, and just after having left Columbus Hospital for the airport the next stented patient had thrombosis! That made a big impact on Colombo, who was going to abolish the anticoagulation regimen for years to come.

The first bear metal stent (BMS) approved in the USA, was the Giantaurco-Rubin stent[14]. Garry Rubin was working at Emory University, Atlanta, and did some animal studies, but at the same time authorised studies on patients. However, he pushed too hard for the time being, got some real problems with the Administration making the stent program almost abolished. Fortunately, hazard wanted that an US Congress Senator suffered from an acute coronary occlusion and Rubin successfully implanted him a stent. The senator made out of it a personal affair and obtained the stent to be officially approved (Rubin-personal communication).

Figure 4. Dr Antonio Colombo and Dr Finci, in front of the poster showing results with half-stent (Palmaz-Schatz) in New Orleans in 1992

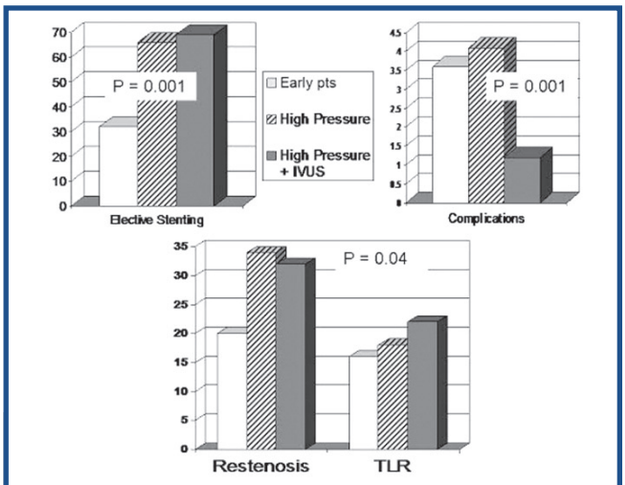


Figure 5. Coronary stenting (BMS) throughout technical evolution: 1992-1999. With the use of IVUS and high balloon pressure there is a change in indications, decrease in complications, with an increase in restenosis and TLR rates with addressing more complex lesions subsets.

BMS

The Palmaz-Schatz stent was a relatively rigid device, at first it had to be hand crimp by the operator on a balloon catheter! The device proved difficulties to be placed at the correct site in tortuous vessel and whan operator tried to pull-back the balloon it was rather a mater of chance that stent stayed on-it. There exists probably no single high-volume operator who has not lost a least one stent in patients' circulation during the PCI at that time, but this phenomenon was largely under reported. In order to improve deliverability, an anecdotal alternative method to stent lesions located in anatomical settings too complex for regular Palmaz-Schatz stent placement was developed in Milan[15]. The method consist of using a disarticulated (one-half) Palmaz-Schatz stent – as a matter of fact, Colombo (Figure 4) „simply" decided to cut a stent by half at the site of articulation! He obtained significant results in delivering the stent on the exact place of coronary lesion.

The world society of interventional cardiology welcomed the arrival of new stent designs e.g technical details of 17 stent models are presented, in the book of P.W. Serruys[16] on coronary stents in 1997. Not only the stent designs and material have evolved over years, but the implantation technique has significantly developed producing a major successful impact. The use of high-pressure balloon inflation (HP), intravascular ultrasound (IVUS) and appropriate antiplatelet therapy have contributed to the abolishment of the need for subsequent anticoagulation, allowing extended stent applications[17,18]. These changes are best shown by Dr Colombo who pioneered this technique[19]. To illustrate that (Figure 5), we compared three groups of patients[20] having stent implantation throughout the period of technical evolution Group A: no IVUS, no HP, with subsequent anticoagulation treatment (n = 434); group B: no IVUS, yes HP, without subsequent anticoagulation treatment (n = 192); and group C: yes IVUS, yes HP, without subsequent anticoagulation treatment (n = 588). The primary success rates were comparable in all groups. There was a clear change in indications for stenting in groups B and C compared with group A (elective stenting: A= 32%; B = 66%; C = 69%; P < 0.0001), in reference vessel size (A = 3.22 mm; B =2.92 mm; C=2.98 mm; P < 0.0001), and for presence of type B2 and C lesions (A = 57%; B = 72%; C = 74%; P < 0.001). The complication rate significantly decreased in group C (A = 3.6%; B = 4.1%; C = 1.2%; P < 0.001) and the mean patient hospital stay decreased to 2 days in groups B and C due to the abolition of the need for anticoagulant treatment. The angiographic restenosis rate increased in groups B and C (A=20%; B =34%; C = 32%; P < 0.001). The need for a repeat procedure increased as stenting of more complex lesions and smaller vessels was attempted: target lesion revascularization (TLR) was performed in 16% of patients in group A, in 18% of group B and in 22% of group C (P= 0.04 for A versus C). Major cardiac events (MACE) occurred in 30-33% in different groups. The evolving technique of coronary stenting has expanded the spectrum of indications and range of coronary vessels attempted, and decreased the complication rates and hospital stay. However, in less-favourable subsets, additional improvements were needed to affect the long-term outcome[21]. These improvements had to wait the introduction of DES.

Indeed, a word should be said about abolishing the anticoagulation treatment – A.Colombo reported the first 80 patients with only aspirin and Ticlopidine treatment after successful stenting in early 1993, just in the course of intensive recruitment of patients for Benestent study, and had a hell of difficulty to convince the European community to adopt the attitude. For example, P. Serruys openly said to him „you will fall from the Himalaya Pick if you are wrong..." and he literary meant that[22]. However, the hard data with IVUS study, corroborated with help of Jonathan Tobis from UCLA led to the international recognition and implementation of Colombo's technique.

Table 1. Devices currently use in percutaneous coronary interventions (PCI) with the year of introduction, advantages and draw-backs

Device	PTCA	BMS	DES	BVS
Year	1977	1986	2001	2009
Advantages	- Simple use - vesel preparation before stenting -known long-term results	- limited need for DAPT - acceptable price	-TLR reduced - improved long-term results compared to BMS	- non permanent implant - avoid late stent thrombosis - establish natural vessel integrity
Draw-backs	- acute complications - restenosis - residual dissection	- TVR 20% -re-occlusion - privent lumen expansion -interface MRI	- stent thrombosis (1-3%) - Incomplete endothelisation (RR 18%) - permanent implant	- «bulky» implant -vessel <2.5mm or >4mm - Long-term results unknown
Restenosis (%) TVR (%)	30-35 (CTO 40) 30-40	20-25 20	7-15 10	N.A. <10 ?
Long-term Success (%)	70-80	85-90	>90	>90-95

BMS = bear metal stent, BVS = bio absorbable vascular scaffold, DAPT= dual antiplatelet treatment, DES = drug eluting stent, MRI= magnetic resonance, PTCA = balloon angioplasty, TVR = target vessel revascularisation

DES

With the expanded indications for the use of BMS, such as being a case in small vessel, long-lesions, bifurcations, and diabetics, two major limitations of BMS became cumbersome: subacute stent thrombosis (ST) and stent restenosis with a need for target vessel revascularization (TVR). The metallic stainless steel cage of BMS stent produced a binary stent restenosis of 35-50% independently of stent model[23]. The brachyterapy was applied in large volume centres – but it was unsuitable (a cathlab in a cathlab!), in particular producing late thrombosis, geographic mismatch, relatively high cost, and requirement of radiation oncologists. Drug-eluting stents (DES) were developed to specifically address the problems of restenosis encountered with BMS (Table 1). The device dispose with three components: metallic platform, polymer coating and antiproliferative drugs (Figure 6).

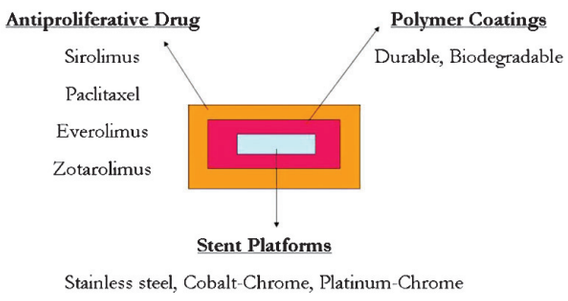


Figure 6. Drug eluting stent (DES) components

The first successful DES trials were using Cypher (Cordis Corp, Johnson and Johnson Company, Miami, FL, USA) which led to its approval[24,25] in Europe in 2002. Soon afterwords, a series of trials enabled commercialisation of paclitaxel eluting Taxus stent (Boston Scientific, Natrick, MA, USA), in 2004. The paclitaxel had somehow higher TLR rate and was used in several studies in the years to come as „non-inferior" stent permiting commercialisation of a new stents of second generation[26], The Xience V (Abbott, IL, USA) everolimus eluting stent was approved and has been available on market since late 2006. The market penetration of stents was very rapid in Switzerland[27], only in the course of the year1996 about 50% of PCI, up to 78% in 2000, and 91% in 2007. Second-generation DES stents have refinod all of the three components: the struts, polymers, and drugs eluted, thereby improved outcomes. Compared with the first generation DES, second-generation devices[28] lowered the risk of ISR, ST, and mortality. For example[29], the Swedish Registry on 94.384 patients found 38% lower risk of restenosis, a 43% lower risk of definite ST, and a 23% lower risk of death compared to first generation DES. Most used second generation stents were Endeavor Resolute (Medtronic) with more biocompatible polymers and Biolimus A9 (Biosense) was a new high-lyophilise sirolimus analogue, and Promus Element (Boston Sc.) everolimus with durable polymer.

Currently, the last generation of stent need only 3 months of DAPT, bioapsorbale coating is only on abluminal side of stent, struts are thin and metallic cage is laser cut hypotube. A novel bio absorbable polymer everolimus-eluting stent Synergy (Boston Sc.) was compared with the durable polymer Promus Element. At follow-up of two years[28], target lesion failure was non-inferior (6.1% for Promus vs. 5.5% for Synergy) with no ST.

There were two events that should be mentioned. In 2006, at the World Congress of Cardiology in Barcelona, E. Camenzind presented[30] the results of a meta-analysis of randomized clinical studies comparing DES versus BMS, reporting greater incidence of total mortality and Q-wave MI for DES (38% versus 16% respectively). Camenzind concluded: „until safer second-generation DES is available, interventional cardiologist should avoid its indiscriminate use"! I was attending the lecture with Dr Colombo who told me while getting out of the conference room: „Thanks good I have got involved in wine[31] production". As a matter of fact, the stent implantation rate went down the first time since introduction of DES. Only in the USA it de-

creased for almost 20% (from 89% at the beginning of 2006 to 70% at the end of the year), as well as in Switzerland (from 82% in 2006 to 71% in 2007).

The second event happened during the American College of Cardiology Meeting in 2007 where result of the „Courage" study were presented at the morning Hot-Session showing equality of stenting versus medical treatment in patients with stable angina[32]. During a panel discussion, the evening before official study presentation, Martin Leon publically discovered the study results, correctly undermining its importance – this made more publicity than the study itself! Dr Leon was suspended from ACC activities for two years, just as an excellent football player.

Industrial involvment

No story in the world is complete without talking about money. The Medinvent stent patent was acquired for about 1 million SFR in 1988 by Schneider Medintag AG, a Swiss company producing balloon catheters, led by Heliane Canepa (who was later honoured the Swiss business woman of the year). The unfavourable result of a multicentre study that followed in 1991 damped this stent for coronary use. The Johnson & Johnson Company (J&J) was the first to market the „Palmaz-Schatz" stent, for a sale price about 2.000 dollars a piece. By 1996 the J&J sold approximate one million stents worldwide with virtually no any competition[33]. Saying that reminds me that, as all authors, I have to relieve my financial disclosures - that unfortunately are none. The market for stents was growing rapidly as coronary stenting overtook PTCA by 1997.

The other medical company, Boston Scientific (BS), which has lost an opportunity to license the Palmaz-Schatz stent, needed a stent to remain a viable player in the field. So, they had explored relations with other small companies owning stent technology. A slotted tube NIR stent has been designed in Israel by Medinol Company of Kobbi Richter. The stent has many technical advantages over Palmaz -Schatz stent, including flexible closed cell design, improved deliverability and flexibility, and length: 35mm long stent compared to 15mm standard. In 1995, BS and Medinol have entered into a series of agreements, followed by a low suite. The NIR Stent was used in Europe in 1996 and introduced to the U.S. two years later. It quickly became a major part of BS business. By year 2000, NIR stent sales have grown to about 600 million dollars in worldwide revenue[34]. As a result, Medinol a small start-up company has become major player. Case settlement was done by 2005 for 750 million dollars.

DES development and numerous new model (about 30 different Stent in Europe), made the market parts to be shared. The J&J announced in 2011 abandoning their coronary stent business, just a year after desperate tentative of buying Connor Medsystems for $1.4B who had developed a beautiful stent model with double drug „reservoirs". The sales of J&J dropped from $2.62 billion in 2006 to only $627 million in 2012, making the end of the successful financial story.

A case of chronic total coronary occlusion (CTO)

The rational of opening chronic occlusion is nowadays extremely well established and the one time scepticism of „having an open artery" is over[35]. Patients with an open artery are not only doing well at medium-term compared to the ones with unsuccessful procedure, but their long-term results up to 20 years are improved. Technical advancement in recanalisation material wires and catheters has allowed for the high procedure success but the long-term benefit after stent implantation is clearly due to the new stent development.

We published one of the first articles that demonstrated benefit in patients with successful PTCA of CTO in Geneva Centre[36]. However, coronary angioplasty of CTO has been associated with disappointing results - primary success was only 60-70% and restenosis rate up to 50% leading to the long term-success in less than half of initially treated population (Figure 6). Technical advancement in wires and material made little impact on results at that time e.g., Magnum wire[37]. The introduction of BMS has improved restenosis rate, still plafond above 20%, with many patients presenting new reclusion at follow-up angiography. The early article in 1995, using BMS published with Dr Colombo, showed still limited improvement with a clinical benefit in about 77% of patients at follow-up[38]. In a Multinational CTO Registry [39] on 1.226 patients followed-up to 5 years, the TLR was lower in DES group compared to BMS group (17.2 versus 31.1%, $p<0.01$). A small Canadian study[40] in 159 patients showed improved event-free survival at 5 years with DES compared to BMS (89.4% versus 74.8% respectively). The advancements in technology of guide-wires, micro-catheters and introduction of retrograde approach for recanalisation, in particular coming from Japan, allowed the success rate to increase substantially (currently in an expert hands close to 90%, O.Katoh – personal communication). At the same time, with systematic implantation of DES long-term result improved with restenosis rate below 10% (Figure 7).

Typical examples are patients with good follow-up results after successful recanalization of CTO at previous BASIC Meeting (ref. workshop summary, 7th Basics Plus, Belgrade, April 11-15, 2011) with the help of our guest-

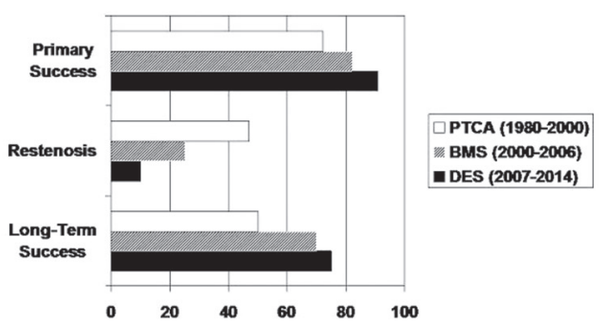


Figure 7. PCI of Chronic Total Coronary Occlusions (CTO). Long-term clinical and angiographic results are improved with development of new stents over time.

operators, G.Sianos, F. Galassi, Saito, J. Ge et al. Not all DES have an equal follow-up result. In one study[41] the everolimus-eluting stents were associated with a significantly lower reocclusion rate than were other drug-eluting stents (3.0% vs. 10.1%; p = 0.001). New DES stents, currently called the 4th generation can even further decrease the recurrence, to less than 10%. The future use of BVS in CTO is certainly challenging, but our excitement at present should be tempered.

Bioresorbable vascular scaffolds (BVS)

Bioresorbable vascular scaffolds (BVS) are intended to overcome most drawbacks of stents: the permanent presence of a metallic cage that stays on the vessel wall beyond its intended purpose preventing acute recoil and late lumen expansion, positive remodelling, impair vessel geometry and normal vasomotor vessel function, and interface with MRI or MRC. A decrease restenosis and stent thrombosis rates as compared with conventional (metallic) stents is possible. Furthermore, the vessel access for eventual future coronary bypass grafting is maintained[42].

The use of BVS has largely been in the context of simple proximal lesions of vessel 2.5-4.0mm in clinical trials, but the indications have expanded to more complex lesions of 'real-world' including long and diffuse disease. At present, three scaffolds models are available for clinical use.

The balloon expandable Absorb device (Abbott Vascular, Santa Clara, California, US) made from semicrystalline poly-L-lactic acid (PLLA) coated with an amorphous poly-D, L-lactide (PDLA) polymer eluting everolimus, has two platinum markers that allow x-ray visualization. The single strut thickness is 156 microns, is desorbed in 2–3 years. The Absorb stent is commercially available in Europe.

The Dreams device (Biotronic, Bulach, Switzerland) is a balloon expandable, paclitaxel-eluting magnesium alloy-based bioresorbable coronary stent. The implant is radiolucent and has a single strut thickness of 125 microns. The absorption process takes 9–12 months. Mechanical properties are similar to the current generation of metallic stents including safe over dilatation. It soon receives a CE mark.

The DeSolve stent (Elixir Medical, Sunnyvale, California, US) provides sufficient radial strength for over 3 months and is fully desorbed in 1–2 years. Self-apposant properties allow to over expanding (for 1 mm without evidence of strut fracture). The Desolve stent received a CE mark in 2013.

Most studies have been done with the Absorb BVS with good clinical results reported up to four years[43]. The Scaffold area by OCT was shown to progressively increase during follow-up with no differences in late lumen loss. The TLR and MACE rates at one-year have been reported as 1.8 and 4.2 %, respectively. Stent thrombosis rate was 0.9 %. The ongoing Absorb III and IV studies (2250 and 3000 patients, respectively) aim to compare Absorb BVS to Xience Everolimus Eluting Stent (Abbott Vascular, Santa Clara, California, US).

The view of BVS antagonists, such as Haim Lotan's from Hadassah Hospital, Israel includes absence of long-term results, current unsuitability for bifurcations, small vessel, or long lesion and of course good result with last generation DES stent. The consensus opinion of Greg Stone is probably the most appropriate at present, keeping with recommended indications for all type of devices[44].

Figure 8. Cardiology School of Belgrade at the Meeting to become BASIC in 2006 (from the right: Prof. Nedeljkovic M, Prof. Ostojic, Prof. Nedeljkovic S., Dr Colombo, Dr Finci, Dr Babic)

Acknowledgments

This article can not be complete without mentioning my Friend, without whom all this would not be possible. I had a chance to be in late '70s in Belgrade, where I did my Master's in Cardiology after successfully accomplishing Medical Military Academy. In early '80s I left for Lausanne, the cradle of coronary interventions, with Ulrich Sigwart the source of my admiration. The time at Geneva University Hospital, with Professor Rutisahuser and Bernhard Meier, the teacher and the pupil of A. Gruentzig the conceiving farther of PTCA, was extremely fruitful and successful with its ups-and-downs; and than comes Antonio Colombo, whose unconditional friendship was both professional and pleasant. Not to forget my „second" home, Belgrade Heart School, my friends since-ever Professors Misa Ostojic and Milan Nedeljkovic, as well as my „professional brothers": G. Stankovic, B. Beleslin, S. Stojkovic, P. Seferovic , with the special tribute to late Prof. Srecko Nedeljkovic (Figure 8). Talking about the „Second" home raises a question of my „first" home[45], but that - that belongs to another story!

References

1. Ruygrok PN, Serruys PW. Intracoronary Stenting: from concept to custom. Circulation 1996; 94 :882-890.
2. Charles Stent (1845-1901) an English. http://circ.ahajournals.org/content/94/5/882.figures-only
3. CV. Ulrich Sigwart. http://en.wikipedia.org/wiki/Ulrich_Sigwart
4. Chateaux Suisse. http://www.bioley-magnoux.ch/typo3/index.php?id=45
5. Topol EJ. Caveats about elective stenting. N Engl J Med 1994;331:539-541.

6. Curfman GD, Morrissey S, Jarcho JA, Drazen JM. Drug-Eluting Coronary Stents. Promise and Uncertainty. N Engl J Med 2007; 356:1059-1060
7. Leo Finci. »Pluritrunkularna koronarna angioplastika », doktorska teza, Medicinski fakultet, Universitet u Beogradu, 1986
8. Finci L, Meier B, Steffenino G, Urban P, Rutishauser W. Restenosis and repeat coronary angioplasty in Geneva. Eur Heart J. 1988;9 Suppl C:11-3.
9. Finci L, Höfling B, Ludwig B, Bulitta M, Steffenino G, Etti H, Meier B. Sulotroban during and after coronary angioplasty. A double-blind, placebo controlled study. Z Kardiol. 1989; 78 Suppl 3:50-4
10. U. Sigwart: Endoluminal Stenting, W. B. Saunders 1996
11. Serruys PW, Strauss BH, Beatt KJ, Bertrand ME, Puel J, Rickards AF, Meier B, Goy JJ, Vogt P, Kappenberger L, Sigwart U. Angiographic follow-up after placement of a self-expanding coronary artery stent. N Engl J Med. 1991; 324:13-17
12. Schatz R. A view of vascular stents. Circulation. 1989; 79:445-457.
13. Schatz RA, Baim DS, Leon M, Ellis SG, Goldberg S, Hirshfeld JW, Cleman MW, Cabin HS, Walker C, Stagg J, Buchbinder M, Teirstein PS, Topol EJ, Savage M, Perez JA, Curry C, Whitworth H, Sousa JE, Tio F, Almagor Y, Ponder R, Penn IM, Leonard B, Levine SL, Fish D, Palmaz JC. Clinical experience with the Palmaz-Schatz coronary stent: initial results of a multicenter study. Circulation. 1991;83:148-161
14. Roubin GS, Cannon AD, Agrawal SK, Macander PJ, Dean LS, Baxley WA, Breland J. Intracoronary stenting for acute and threatened closure complicating percutaneous transluminal coronary angioplasty. Circulation. 1992; 85:916-927.
15. Colombo A, Hall P, Thomas J, Almagor Y, Finci L. Initial experience with the disarticulated (one-half) Palmaz-Schatz stent: a technical report. Cathet Cardiovasc Diagn 1992; 25(4):304-8.
16. Serruys PW. Handbook of coronary stents. Martin Dunitz Ltd 1997
17. Colombo A, Finci L. A simple step towards better stent deployment. J Invasive Cardiol 2002; 14(5):227-9.
18. Nakamura S, Colombo A, Gaglione S, Almagor Y, Goldberg SL, Maiello L, Finci L, Tobis JM. Intracoronary ultrasound observations during stent implantation. Circulation. 1994; 89: 2026-2034
19. Colombo A, Hall P, Nakamura S, Almagor Y, Maiello L, Martini G, Gaglione A, Goldberg SL, Tobis JM. Intracoronary stenting without anticoagulation accomplished with intravascular ultrasound guidance. Circulation. 1995; 91: 1676-1688.
20. Finci L, Ferraro M, Kobayashi Y, Gregorio Jd J, Moussa I, Albiero R, Di L, Kobayashi N, Martini G, Tucci G, Recchia M, Di Mario C, Colombo A. Coronary stent implantation throughout technical evolution: immediate and follow-up results. Int J Cardiovasc Intervent 1998;1(1):29-39.
21. Finci L, Ferraro M, Nishida T, Albiero R, Corvaja N, Vaghetti M, Stankovic G, Recchia M, Di Mario C, Colombo A. Coronary stenting beyond standard indications. Immediate and follow-up results. Ital Heart J. 2000; 1(11):739-48.
22. Serruys PW. Navigating stent era from bare metal to drug eluting stent. The transformation of PCI. Plenary Session 12, State of the art lecture. European Congress of Cardiology, 2013.
23. Huibregtse B, Granada JF. New DES Platforms. Does the metal alloy matter. Cardiac Interventions Today. 2011; 35-38
24. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P, Belardi J, Sigwart U, Colombo A, Goy J-J, van den Huevel P, Delcan J, Morel MA, for the BENESTENT Study Group. A comparison of balloon expandable stent implantation with balloon angioplasty in patients with coronary artery disease. N Engl J Med 1994;331:489-495
25. Fischman DL, Leon MB, Baim D, Schatz RA, Penn I, Detre K, Savage MP, Veltri L, Ricci D, Nobuyoshi M, Cleman M, Heuser R, Almond D, Teirstein P, Fish D, Colombo A, Brinker J, Moses J, Hirshfeld J, Bailey S, Ellis S, Rake R, Goldberg S. A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease. N Engl J Med 1994; 331:496-501.
26. Bertrand M, Regnier C. Major Advances in Cardiology. L.E.N. Medical Paris France 2012
27. Maeder MT, Windecker S, Roffi M, Kaiser CA, Stauffer JC, Pedrazzini G, Rickli H. Interventional cardiology in Switzerland during the year 2007. Kardiovasculare Medizin 2010; 13(1) 18-24
28. Meredith IT, Verheye S, Weissman NJ, Barragan P, Scott D, Valdés Chávarri M,West NE, Kelbæk H, Whitbourn R, Walters DL, Kubica J, Thuesen L, Masotti M,Banning A, Sjögren I, Stables RH, Allocco DJ, Dawkins KD. Six-month IVUS and two-year clinical outcomes in the EVOLVE FHU trial: a randomised evaluation of a novel bioabsorbable polymer-coated, everolimus-eluting stent. EuroIntervention 2013; 9(3):308-15.
29. Sarno G, Lagerqvist B, Frobert O, et al. Lower risk of stent thrombosis and restenosis with unrestricted use of new-generation drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). Eur Heart J 2012; 33:606-13.
30. Camenzind E, Steg PG, Wijns W. Stent thrombosis late after implantation of first-generation drug-eluting stents: a cause for concern. Circulation. 2007; 115(11):1440-55;
31. A. Colombo, wine production. http://www.colombovino.it/en/
32. Diamond GA, Kaul S. COURAGE under fire: on the management of stable coronary disease. J Am Coll Cardiol. 200;50(16):1604-9.
33. Read more: http://medcitynews.com/2011/06/end-of-jj-stent-business-carries-lessons-for-medical-device-innovators/#ixzz2wa6zYtF8
34. Harvard Law. http://weblaw.usc.edu/assets/docs/contribute/MedicalStent.pdf
35. Reifart N. Chronic total coronary occlusion percutaneus intervention. Eur Hear J 2014; 9 :1139-1140
36. Finci L, Meier B, Favre J, Righetti A, Rutishauser W. Long-term results of successful and failed angioplasty for chronic total coronary arterial occlusion. Am J Cardiol 1990; 66(7):660-2.
37. Meier B, Carlier M, Finci L, Nukta E, Urban P, Niederhauser W, Favre J. Magnum wire for balloon recanalization of chronic total coronary occlusions. Am J Cardiol 1989; 64(3):148-54.
38. Goldberg SL, Colombo A, Maiello L, Borrione M, Finci L, Almagor Y. Intracoronary stent insertion after balloon angioplasty of chronic total occlusions. J Am Coll Cardiol 1995; 26(3):713-9.
39. Mehran R, Claessen BE, Godino C, Dangas GD, Obunai K, Kanwal S, Carlino M,Henriques JP, Di Mario C, Kim YH, Park SJ, Stone GW, Leon MB, Moses JW, Colombo A; Multinational Chronic Total Occlusion Registry. Long-term outcome of percutaneous coronary intervention for chronic total occlusions. JACC Cardiovasc Interv 2011;4(9):952-61.
40. De Felice F, Fiorilli R, Parma A, Musto C, Nazzaro MS, Scappaticci M, Confessore P, Guerra E, Belloni F, Violini R. Five-year outcomes in patients with chronic total coronary occlusion treated with drug-eluting vs bare-metal stents: a case-control study. Can J Cardiol 2013;29(8):945-7.
41. Valenti R, Vergara R, Migliorini A, Parodi G, Carrabba N, Cerisano G, Dovellini EV, Antoniucci D. Predictors of reocclusion after successful drug-eluting stent-supported percutaneous coronary intervention of chronic total occlusion. J Am Coll Cardiol 2013;61(5):545-50.
42. Syllabus JIM 2014, Rome, Italy 14-18 Feb 2014
43. Serruys PW, BVS Extend: An Interim Report on the 12-Month Clinical Outcomes from the First 450 Patients Registered, Presented at: Euro PCR, Paris, France, 21–24 May 2013.
44. Stone GW. Bioresorbable vascular scaffolds: is imaging everything? Euro Intervention 2014 Mar 20;9(11):1255-7.
45. Finci Z. Sefardski Nocturno. Veselin Maslesa Pbl. Sarajevo, 1990. ISB 86-21-0042244

Srce i krvni sudovi 2014; 33(1): 8-12

Pregledni rad

Radiation safety in the cardiac catheterization laboratory: our responsibility to change

[1]Eugenio Picano, [2]Emanuela Piccaluga, [3]Renato Padovani, [4]Claudio Antonio Traino, Maria Grazia Andreassi, [5]Giulio Guagliumi

[1]CNR, Institute of Clinical Physiology, Pisa, Italy; [2]Cardiology Unit, Hospital Sacco, Milan, Italy; [3]Medical Physics Department, University Hospital, Udine, Italy; [4]Division of Health Physics University Hospital of Pisa, Pisa, Italy; [5]Interventional Cardiology Unit, Ospedale Papa Giovanni XXIII, Bergamo, Italy

Abstract Medical radiation from x-rays and nuclear medicine is the largest manmade source of radiation exposure in Western countries, and accounts for a mean effective dose of 3.0 milliSievert (mSv) per person per year, equivalent to the radiological risk of 150 chest x-rays. Of these, 0.43 mSv come from interventional radiology (0.20 mSv) and interventional cardiology (0.23 mSv). Among adult cardiology patients, fluoroscopically-guided diagnosis and intervention account for 12% of all radiological examinations performed, and 48% of their total collective dose. On average, a diagnostic invasive angiogram corresponds to a patient radiation exposure of about 7 mSv (range 2-16), while coronary stenting corresponds to 15 mSv (range 7-57). Progressively higher effective doses are observed for transcutaneous aortic valvuloplasty (39 mSv), dilation of total occlusion of coronary arteries (81 mSv, range 17-194) and endovascular thoraco-abdominal aneurysm repair procedure (76-190 mSv). Most experienced (and most exposed) interventional cardiologists have an exposure per annum of around 5 mSv, two to three times higher than diagnostic radiologists, with a typical cumulative lifetime cumulative exposure around 100 mSv and attributable risk in the order of magnitude of 1 cancer (fatal and non-fatal) per 100 exposed subjects. However, adequate radiation protection training and diligent protection can reduce this radiation exposure by 90%. Attention to radiation protection is one aspect – and not the least important – of good practice of interventional cardiology.

Key words cancer, catheterization, radiation, responsibility, sustainability

Introduction

Over the last 20 years, invasive fluoroscopy and interventional cardiology have expanded significantly in the field of diagnostic studies, interventions, and device implantation. The effective dose (ED) to patients in invasive fluoroscopy procedures can range anywhere from 1 to 100 milliSievert (mSv), equivalent to a radiological risk corresponding to 50 to 5000 chest x-rays[1]. The occupational exposure of interventional cardiologists can be two to three times higher than that of diagnostic radiologists[2,3]. The increasing use and complexity of interventional cardiology techniques have not been matched by increasing awareness and knowledge by prescribers and practitioners. Most doctors – including invasive cardiologists – grossly underestimate the radiation doses for most commonly requested tests[4,5]. However, this knowledge is crucial for several reasons. First, the dose is proportional to long-term cancer risk, and therefore one must be aware of the dose in order to perform a proper risk-benefit assessment, quintessential for evaluating the appropriateness of any given test or procedure. Second, knowing the dose is necessary in order to apply dose optimization, intended to achieve the desired diagnostic information or therapeutic benefit with the lowest necessary dose. Third, radiation awareness is essential for better protection of interventional cardiologists and staff (technicians and nurses), since simple radioprotection knowledge can reduce occupational exposure by tenfold, making one's professional life longer and healthier. These are three excellent reasons to pursue a policy of radioprotection in the cardiac catheterization lab[6-8].

Deterministic and stochastic risks in the cardiac catheterization lab

There are two main biological effects of radiation: tissue reactions (deterministic effects), which occur when the radiation dose exceeds a specific threshold and become evident days to months after exposure as a predictable change in tissue occurs, and stochastic effects, which relate to the potential for future harm to the tissue and the body[9,10].

Correspondence to Eugenio Picano, MD, PhD, CNR, Institute of Clinical Physiology, Via Moruzzi, 1, 56124 Pisa, Phone: 0039 050 3152398, Email: picano@ifc.cnr.it

Table 1. Doses of common examinations in the cardiac catheterization lab

	Invasive Fluoroscopy	Effective dose (mSv)	Equivalent CXRs
ADULT	Diagnostic coronary angiography	7 (2-16)	350
	PCI	15 (7-57)	750
	Thoracic angiography (pulmonary or aorta)	5 (4-9)	250
	Abdominal angiography or aortography	12 (4-48)	600
	Pelvic vein embolization	60 (44-78)	3000
	TIPS placement	70 (20-180)	3500
	Aortic valvuloplasty	39	1950
	Dilation chronic coronary occlusion	81 (17-194)	4050
	ETAAAR procedure	76-119	3800-5950
	Renal angioplasty	54	2700
	Iliac angioplasty	58	2900
PEDIATRIC	Diagnostic cardiac catheterization	6.0 (0.6-23.2)	Age-dependent
	Closure of ASD	2.8 (1.8-7.4)	Age-dependent
	Patent ductus arteriosus occlusion	7.6 (2.1-37)	Age-dependent
	Balloon valvuloplasty	8.1 (2.9-20)	Age-dependent

Deterministic (tissue reaction) effects of most concern for patients and operators include skin injuries (reported in patients during long, repeated and complicated interventional procedures). The severity of tissue reactions, rather than probability of occurrence, is proportional to the dose imparted to the tissue. Patient skin injuries may occur when fluoroscopic procedures exceed 20 min using high-contrast fluoroscopy mode, or 60 min in low-level fluoroscopy. Tissue injury following fluoroscopic guided procedures remains asymptomatic and often goes unrecognized as it occurs weeks after the procedure. They usually occur on the patient's back (where the x-rays are delivered) and many severe cases come to light only through litigation[11]. A case is filed in the US courts every 4 to 5 weeks by patients who have suffered such injuries[12].

The lens is a radiosensitive tissue, and thus cataract formation is the primary ocular complication associated with ionizing radiation exposure for both patients and doctors. Until recently, the dose threshold for radiation-induced lens opacities was considered 2 Sv for a single dose or 5 Sv for fractionated dose. Currently, radiation-induced cataract, previously thought to be deterministic (tissue reaction), is now recognized to be possibly stochastic in nature, occurring at a much lower radiation exposure level than previously thought. Indeed, several epidemiological studies showed an increased incidence of lens opacities at doses below 0.5 Sv. Accordingly, on April 21, 2011 the International Commission on Radiological Protection (ICRP) slashed the earlier dose limit of 150 mSv in a year for the lens of the eye, to the present 20 mSv in a year, averaged over a defined period of 5 years, with no single year exceeding 50 mSv[13]. Eye cataracts, with the radiation-specific type of posterior sub-capsular opacities, can be observed in one-third of staff after 30 years of work – as a consequence of lack of specific protection and too-permissive limits allowed for the current generation of workers up to 2011[14].

The stochastic effect of most concern is a carcinogenic effect (in both exposed patients and doctors). It occurs when the cell is modified by damage to its DNA but remains viable, the harm eventually being expressed through cell proliferation. Ionizing radiation damages DNA molecules either directly (though ionization of the DNA molecule) or indirectly (through generation of free radicals and reactive oxygen species in the surrounding medium). Cancer occur after a latency period of many years. Reducing the risk of cancer is at the core of the radioprotection system for patients and staff[15].

Radiation doses

The radiation doses of common invasive fluoroscopy examinations are reported in Table 1. As a reference dose, a conventional chest radiography (single postero-anterior projection) corresponds to 0.02 mSv; a 64-slice coronary CT to 15 mSv (3-32) and a Sestamibi Myocardial Perfusion Scintigraphy to 9.4 mSv[1].

On the equipment's display, values are usually reported as a dose-area product (DAP) or Kerma-area products (KAP) indicating total energy impacting the patient for a given procedure. As a general rule, ED can be estimated approximately as follows: ED (mSv) = DAP (Gy x cm^2) x 0.2 (mSv/Gy cm^2). The conversion factor (from DAP to mSv) is age-specific, and increases with decreasing age. In adults, the dose in mSv = DAP (Gycm2) x 0.2. Consequently, DAP quantity represents a relevant dosimetry index, the value of which should be optimized against the diagnostic reference level, which varies for each procedure and can be used as a tool to comply with the ALARA (As Low As Reasonably Achievable) principle[1].

The many factors modulating the dose in the cardiac cath lab are summarized in Table 2 and can reduce the dose by a factor of 10 to 100[16-18].

Protection of personnel

Protection of doctors is just as important as the protection of patients. Most experienced (and most exposed) cardiac electrophysiologists have an exposure per annum of around 5 mSv, two to three times higher than diagnostic radiologists, with a typical cumulative

Table 2. Factors modulating doses in the cardiac catheterization laboratory

		Lower doses	Higher doses
Operator-dependent	Operator background	Expert	Beginner
	Cath lab director	Radiation aware	Not radiation aware
	Written records	Includes KAP	Omits KAP
	Arterial approach	Transfemoral	Transradial
	Pulsed fluoroscopy rate	Low (≤ 12.5 fps)	High (> 12.5 fps)
	Patient to intensifier distance	Small	Large
	Ventriculography	No	Yes
	Cine-duration	Short	Long
	Magnified views	Few	Many
	Projection	Ant, RAO	Lateral, LAO
	Dose audit	Yes	No
Patient-dependent	Body habitus	Lean	Obese
	Coronary lesion to be dilated	Simple, single	Complex, multiple
Technology-dependent	X-ray system	inspected for QC	Not tested for QC

RAO: Right Anterior Oblique projection; LAO: Left Anterior Oblique projection; KAP: Kerma Area Product; QC: quality control

lifetime attributable risk on the order of magnitude of 1 cancer (fatal and non-fatal) per 100 exposed subjects[3]. Operator dose per procedure correlates somewhat with the patient dose, but may be typically 1000 times lower depending upon the shielding employed (one unit of incidence scatter dose for the operator when 1000 units of incidence dose are given to the patient). However, adequate radiation protection training and diligent protection can reduce this radiation exposure by 90%[19].

The order of magnitude and risks

A cumulative ED of 100 mSv may be reached by a patient after four ablation procedures plus two or three CT's, with an extra-risk of cancer of 1 in 100. The same cumulative dose of 100 mSv can be reached by an experienced invasive cardiologist after 30 years of work. This is a „population" risk, and the true individual risk is dictated – as always in medicine – by genetic and environmental factors. For instance, the average dose of 15 mSv confers a risk of one extra-cancer in every 750 exposed 50-year-old male patients, but the risk is 38% higher in women, must be multiplied by 4 in children, and is reduced by 50% in an 80-year-old man. The risk is higher in presence of some unfavorable polymorphisms of genes involved in DNA repair and in presence of other environmental carcinogens such as smoking[20,21]. The risk can probably be reduced with chemoprotective strategies, for instance with anti-oxidant cocktails[22], although the cost-benefit assessment of these strategies remains unsettled.

The use of fluoroscopy during invasive fluoroscopy intervention (such as catheter radiofrequency ablation) is likely to result in a small increase in the lifetime risk of a fatal malignancy, and the most likely malignancies will be lung, bone marrow (leukemia) and the breast, the organs exposed to the maximum amount of radiation[23].

The risk may be acceptable when flanked with a documented or expected benefit, but it is not negligible, and should be spelled out in the informed consent form before the procedure[24]. After the examination, the actual dose delivered should be stored in the patient's and laboratory's records. This simple process will gently force the doctor to learn what he/she should already know, enabling him/her to make more responsible choices[25].

Novel opportunities in the cardiac catheterization laboratory

The challenges of radioprotection in the cardiac catheterization lab opens exciting new opportunities for the clinician, the clinical scientist, and the pharma and technology industries, in a perspective that will rapidly positively impact on both patients and doctors[26].

For the clinician, the simple adoption of a radiation history to be included in medical records will modify the current clinical perspective. Cumulative radiation exposure is a recognized risk factor for cancer and probably for atherosclerosis[27], and a dedicated radiation history should be systematically collected in the medical records[28-30]. The step-up in the quality of this section of the records is linked to the progressive shift from reference dose to truly delivered doses for that patient in the specific examinations. This will increase the quality of the clinical information, serve as feedback for the patient on the quality of care received, and eventually lead the physician and the interventional cardiologist towards a radiation-conscious practice.

For the interventional cardiologist, the possibility of becoming familiar with novel radiation-sparing approaches will open new professional opportunities. For instance, one possible strategy for reducing radiation exposure in the pediatric population is to use X-ray magnetic resonance fusion, with 30% reduction in contrast dose and radiation dose - albeit with longer anesthesia time[31].

For the researcher, it is essential to move from the current evidence-poor to an evidence-rich milieu, with data directly linking radiation exposure to cancer and

Table 3. Radiation in the cath lab: our responsibility to change

		What we have	What we need
PATIENT	Dominant culture	More (exams) is better	Less (dose) is more
	Keep record	Number of test	Dose of each
	Radiation history	Absent	Present
	Informed consent	Ignored	Spelled-out
	Received dose in report	Missing	Mandatory
	Dose coding	KAP or DAP	Effective dose (mSv)
	Dose	Ignored	Considered
DOCTOR	Technology upgrading	More short-term cost	Less long-term risk
	Lowering dose	A curiosity for physicist	Preventing cancer
	The cancer risk	Theoretical	A professional risk
	What can protection do	Reduce work comfort	Allow to live longer
	Dose reading	Off-line, months after	On-line, real time
	Risk of the staff	Population-based	Personalized
SCIENTIST	Risk estimation	Population-based	Tailored
	Epidemiological data on staff	Nuclear plant workers	Cath lab workers
	Epidemiological data on pts	Children with CT	CHD patients
	Focus on risks	Only Cancer risks	Non-cancer risks

CHD: congenital heart disease, CT: Computerized Tomography

non-cancer (including arterial and brain premature aging) effects in our patients and in ourselves as exposed population. In particular, the interventional cardiology community should play a proactive role in collecting new evidence. In the USA, the Multispecialty Occupational Health Group network triggered a cohort mortality study comparing cancer and other serious disease outcomes (including cardiovascular disease) in 44,000 physicians performing fluoroscopically guided procedures (including interventional cardiologists, cardiac electrophysiologists, radiologists, neuroradiologists and others)[32]. In Italy, the Healthy Cath Lab study is organized by the Italian National Research Council–Institute of Clinical Physiology with endorsement by the Italian Society of Invasive Cardiology. The Italian study population will involve 500 exposed interventional cardiologists and staff (technicians and nurses) evaluated by a molecular epidemiology approach to assess „early warning signs" of brain and vascular aging.

For the industry, there is growing interest in new textile materials for better and more ergonomic shielding for patients and doctors, also based on novel alloys and nano-technology. Novel solutions for real-time dosimetry for doctors and exact organ dose assessment for patients are being actively investigated and have great potential to become game-changers in the device market, as is happening in electrophysiology with new techniques for near-zero exposure based on non-fluoroscopic navigation in electrophysiology.

Finally, the patient will benefit from these innovations, since in the end radiation doses will drop and the benefit will remain the same, making the cardiac catheterization lab a safer place. Radioprotection will mainly benefit the invasive cardiologist, who will realize that the strict application of very basic principles of radioprotection – time, shielding and distance principles – will make his/her life healthier and longer. The amount of radiation exposure decreases with the shorter time of use of radiation and with the greater distance from the radiation source and the patient. As a rule, by doubling the distance, one reduces the exposure by a factor of 4. Several items can aid in shielding, which can reduce exposure by a factor of 10: leaded aprons of course, but also special glasses to protect from cataract formation, thyroid collars, and ceiling-mounted overhead radiation shields. In many catheterization laboratories, these resources do not exist -- or are not employed routinely[33].

Conclusions

The advent of radioprotection culture in the cardiac catheterization lab is a unique opportunity for today's generation of professionals, who have the responsibility to change time-honored radiation-insensitive practices that increase the risk to patients and to us without any benefit (Table 3). The key messages are simple:

1. Attention to radioprotection is one aspect – and not the least important – of good practice of interventional cardiology.

2. Protecting the patient from an unjustified or unoptimized dose is the best way to protect yourself and your staff.

3. Before the exam, both you and the patient should know the expected delivered dose (which is directly proportional to the long-term risk).

4. During the exam, make every effort to keep the dose as low as possible.

5. After the exam, write the dose down in the records. You and your patient need to know it, because short-term (weeks or months) deterministic (skin ulcers) and long-term (years or decades) stochastic (cancer) risk depend on it.

And finally: a smart interventional cardiologist cannot be afraid of radiation, but must be very afraid of radiation unawareness[1].

References

1. Picano E, Vañó E, Rehani MM, Cuocolo A, Mont L, Bodi V, Bar O, Maccia C, Pierard L, Sicari R, Plein S, Mahrholdt H, Lancellotti P, Knuuti J, Heidbuchel H, Di Mario C, Badano LP. The appropriate and justified use of medical radiation in cardiovascular imaging: a position document of the ESC Associations of Cardiovascular Imaging, Percutaneous Cardiovascular Interventions and Electrophysiology. Eur Heart J 2014;35:665-672.
2. Vañó E, González L, Guibelalde E, Fernández JM, Ten JI. Radiation exposure to medical staff in interventional and cardiac radiology. Br J Radiol 1998;71:954-960.
3. Venneri L, Rossi F, Botto N, Andreassi MG, Salcone N, Emad A, Lazzeri M, Gori C, Vano E, Picano E. Cancer risk from professional exposure in staff working in cardiac catheterization laboratory: insights from the National Research Council's Biological Effects of Ionizing Radiation VII Report. Am Heart J 2009;157:118-124.
4. Correia MJ, Hellies A, Andreassi MG, Ghelarducci B, Picano E. Lack of radiological awareness among physicians working in a tertiary-care cardiological centre. Int J Cardiol 2005;103:307-311.
5. Kim C, Vasaiwala S, Haque F, Pratap K, Vidovich MI. Radiation safety among cardiology fellows. Am J Cardiol 2010;106:125-128.
6. Hirshfeld JW Jr, Balter S, Brinker JA. et al. American College of Cardiology Foundation; American Heart Association/; HRS; SCAI; American College of Physicians Task Force on Clinical Competence and Training (2005). ACCF/AHA/HRS/SCAI clinical competence statement on physician knowledge to optimize patient safety and image quality in fluoroscopically guided invasive cardiovascular procedures: a report of the American College of Cardiology Foundation/American Heart Association/ American College of Physicians Task Force on Clinical Competence and Training. Circulation 111:511-532.
7. Picano E, Vañó E. Radiation exposure as an occupational hazard. EuroIntervention 2012;8:649-653.
8. Heidbuchel H, Wittkampf F, Vano E, Ernst S, Schilling R, Picano E, Mont L. Practical ways to reduce radiation dose for patients and staff during device implantations and electrophysiological procedures. EHRA Position Paper. Europace 2013. doi:10.1093/europace/eut409.
9. BEIR VII Health Risks from Exposure to Low Levels of Ionizing Radiation, Phase 2. http://www.nap.edu/openbook.php?isbn=030909156X. Retrieved: February 17th, 2014
10. Report of the United Nations Scientific Committee on the Effects of Atomic Radiation 2010. Fifty-seven session: Summary of Low-dose Radiation Effects on Health. Wien, May 2011. http://www.unscear.org/docs/reports/2010/UNSCEAR_2010_Report_M.pdf
11. Frazier TH, Richardson JB, Fabré VC, Callen JP. Fluoroscopy-induced chronic radiation skin injury: a disease perhaps often overlooked. Arch Dermatol 2007;143:637-640.
12. Rehani MM, Srimahachota S. Skin injuries in interventional procedures. Radiat Prot Dosimetry 2011;147:8-12.
13. Stewart FA, Akleyev AV, Hauer-Jensen M, Hendry JH, Kleiman NJ, Macvittie TJ, Aleman BM, Edgar AB, Mabuchi K, Muirhead CR, Shore RE, Wallace WH. ICRP statement on tissue reactions and early and late effects of radiation in normal tissues and organs—threshold doses for tissue reactions in a radiation protection context. Ann ICRP 2012;41:1-322. Authors on behalf of ICRP, doi:10.1016/j.icrp.2012.02.001.
14. Rehani MM, Vano E, Ciraj-Bielac O, Kleiman NJ. Radiation and cataract. Radiat Prot Dosimetry 2011;147:300-304.
15. Radiation Protection 125. Low dose ionizing radiation and cancer risk. Luxembourg, 2001 http://ec.europa.eu/energy/nuclear/radiation_protection/doc/publication/125.pdf
16. Bernardi G, Padovani R, Morocutti G, Vañó E, Malisan MR, Rinuncini M, Spedicato L, Fioretti PM. Clinical and technical determinants of the complexity of percutaneous transluminal coronary angioplasty procedures: analysis in relation to radiation exposure parameters. Catheter Cardiovasc Interv 2000;51:1-9.
17. Vañó E. Radiation exposure to cardiologists: how it could be reduced. Heart 2003;89:1123-1124.
18. Rehani M, Ciraj Bjekac O, Vañó E, Miller DL, Walsh S, Giordano BD, Perslinden J. Radiological protection in fluoroscopically guided procedures performed outside the imaging department. ICRP Publication 117. Ann ICRP 2010;40:1-102.
19. Vaño E, Gonzalez L, Fernandez JM, Alfonso F, Macaya C. Occupational radiation doses in interventional cardiology: a 15-year follow-up. Br J Radiol 2006;79:383-388.
20. Andreassi MG, Cioppa A, Botto N, Joksic G, Manfredi S, Federici C, Ostojic M, Rubino P, Picano E. Somatic DNA damage in interventional cardiologists: a case-control study. FASEB J 2005;19:998-999.
21. Andreassi MG, Foffa I, Manfredi S, Botto N, Cioppa A, Picano E. Genetic polymorphisms in XRCC1, OGG1, APE1 and XRCC3 DNA repair genes, ionizing radiation exposure and chromosomal DNA damage in interventional cardiologists. Mutat Res 2009;666:57-63.
22. Andreassi MG, Cioppa A, Manfredi S, Neri MG, Foffa I, Picano E. N-acetyl cysteine reduces chromosomal DNA damage in circulating lymphocytes during cardiac catheterization procedures: a pilot study. Int J Cardiol 2012;161:93-96.
23. Kovoor P, Ricciardello M, Collins L, Uther JB, Ross DL. Risk to patients from radiation associated with radiofrequency ablation for supraventricular tachycardia. Circulation 1998;98:1534-1540.
24. Picano E. Informed consent and communication of risk from radiological and nuclear medicine examinations: how to escape from a communication inferno. Education and debate. BMJ 2004;329:849-851.
25. Terranova G, Ferro M, Carpeggiani C, Recchia V, Braga L, Semelka RC, Picano E. Low quality and lack of clarity of current informed consent forms in cardiology: how to improve them. JACC Cardiovasc Imaging 2012;5:649-655.
26. Picano E, Vañó E. The radiation issue in cardiology: the time for action is now. Cardiovasc Ultrasound 2011;9:35.
27. Borghini A, Gianicolo EA, Picano E, Andreassi MG. Ionizing radiation and atherosclerosis: current knowledge and future challenges. Atherosclerosis 2013;230:40-47.
28. Picano E. Sustainability of medical imaging. Review. Brit Med J 2004; 328:578-580.
29. The Creative Destruction of Medicine: How the Digital Revolution Will Create Better Health Care by Eric Topol. Basic Books, New York, 2012.
30. Conti CR. Radiation awareness. An appeal is made for including radiation exposure in a patient's medical records. Eur Heart J 2014; 35:600-601.
31. Abu Hazeem AA, Dori Y, Whitehead KK, Harris MA, Fogel MA, Gillespie MJ, Rome JJ, Glatz AC. X-ray magnetic resonance fusion modality may reduce radiation exposure and contrast dose in diagnostic cardiac catheterization of congenital heart disease. Catheter Cardiovasc Interv 2014 Mar 12. doi: 10.1002/ccd.25473
32. Linet MS, Kim KP, Miller DL, Kleinerman RA, Simon SL, Berrington de Gonzalez A. Historical review of occupational exposures and cancer risks in medical radiation workers. Radiat Res 2010;174:793-808.
33. Roguin A. CardioPulse Articles . Radiation in cardiology: can't live without it! Eur Heart J 2014;35:599-604.

Srce i krvni sudovi 2014; 33(1): 13-20

Pregledni rad

Standardize Transcatheter Aortic Valve Implantation with CoreValve self expandable prosthesis and post procedurals management

Gian Paolo Ussia, Valeria Cammalleri, Francesco Romeo

Università degli Studi di Roma „Tor Vergata", Italy

Transcatheter aortic valve implantation (TAVI) is a therapeutic alternative to surgical aortic valve replacement (SAVR) or palliative medical therapy for patients with symptomatic severe aortic valve stenosis (AVS)[1-5]. The high surgical risk for a patients with aortic valve stenosis has to be assessed jointly with the cardiac surgeon and the cardiac anaesthesiologist, as indicated in the guidelines for valvular heart disease management issued by the European society of cardiology in 2012[6]. Results from registries and trial are favourable with unexpected results of prosthesis performance and survival rate at 3 and 5 years of follow up[7-13].

TAVI carries higher risk of post procedural adverse events than conventional percutaneous cardiovascular interventions, due to the baseline clinical condition of the patients and to the associated comorbidities.

Therefore, careful patient monitoring in a intensive care unit (ICU) during the first 48 hours seems to be extremely important to early detect and manage complications, as well as decrease the rate of adverse events and the length of in-hospital stay.

Preprocedural patient assessment

Pre-procedure evaluation include transthoracic echocardiography, invasive cardiac evaluation with right and left cardiac catheterization, coronary angiography and cardiac and vascular multislice computed tomography (MSCT). The baseline risk of the patients population is estimated by the logistic EuroScore, EuroScore II and STS-PROM score[14-18]. Adjunctive risk criteria, not included in these scores are frailty, porcelain aorta, severe liver disease/cirrhosis, hostile chest, severe right ventricle dysfunction, chest radiation, degenerative neurological disorders, patent internal mammary artery or other critical conduits adherent to the sternum, severe right ventricle dysfunction, or any contraindication to extracorporeal circulation[19]. Transthoracic or transesophageal echocardiography are needed to diagnose the aortic stenosis, assess the left ventricular function, characterize the other valves, and determinate pulmonary pressure. These elements are of paramount importance for planning the procedure and stratify the procedural risks (figure 1). Furthermore MSCT plays a crucial role in the screening of

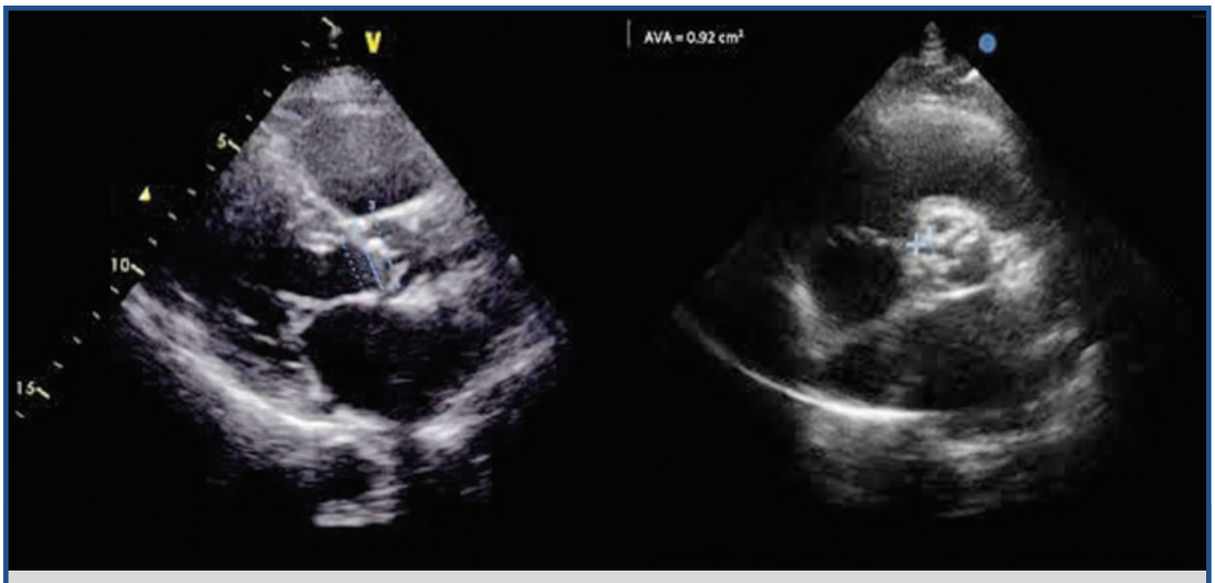


Figure 1. Transthoracic echocardiogram in parasternal long-axis and short-axis view. The aortic valve is examined, with particular attention to the left ventricular outflow tract diameter (1), annulus (2) and sinus of Valsalva width (3). Valvular calcium distribution and planimetric artic valve area (AVA) are also assessed.

Correspondence to Gian Paolo Ussia, MD, Department of Cardiovascular Disease, Tor Vergata University of Rome, Rome, Italy, Viale Oxford, 81; 00133 Rome, e-mail: Gian.Paolo.Ussia@uniroma2.it , phone: 00390620904009, fax 00390620904008

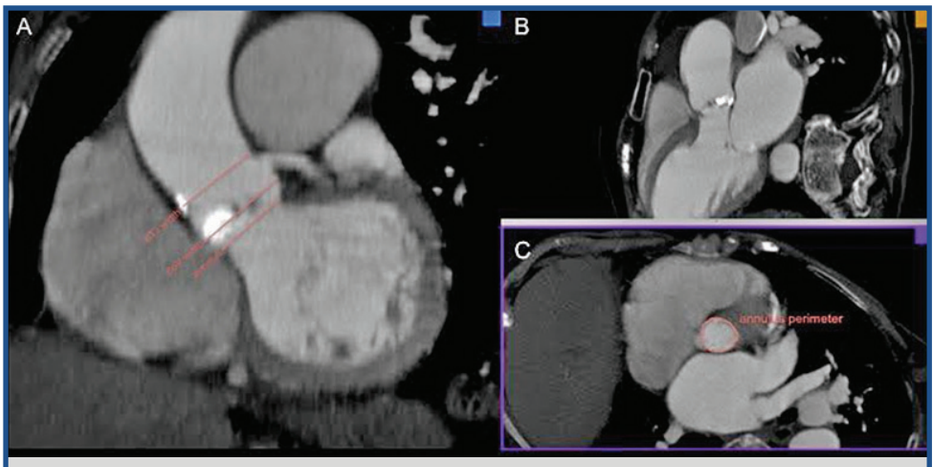


Figure 2. Multiplanar reconstruction of a cardiac MSCT. The three planes are examined. A) Coronal plane the left ventricular outflow tract, aortic annulus, sinus of Valsalva, sinu-tubular junction and coronary take off are measurable; B) sagittal plane, ascending aorta visualization and it helps for optimal orientation of the coronal plane; C) transversal plane, the perimeter of the aortic valve annulus is measured in this view.

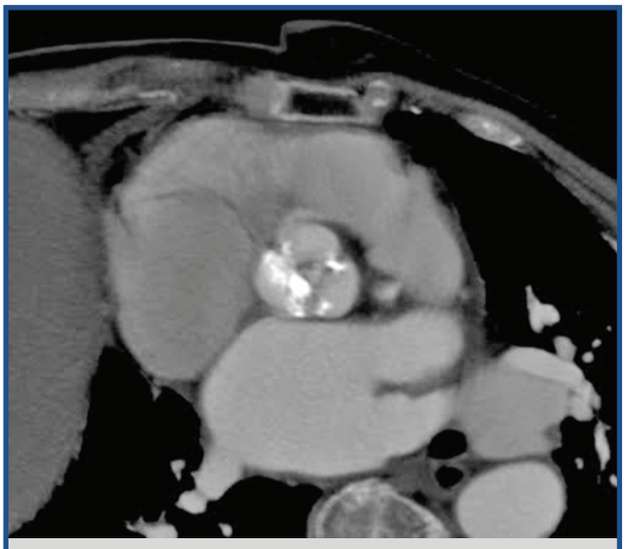


Figure 3. Transversal plane of multiplanar reconstruction of a cardiac MSCT. This projection allow to determinate the anatomy of the cusps, to rule out bicuspid valve and evaluate calcium distribution.

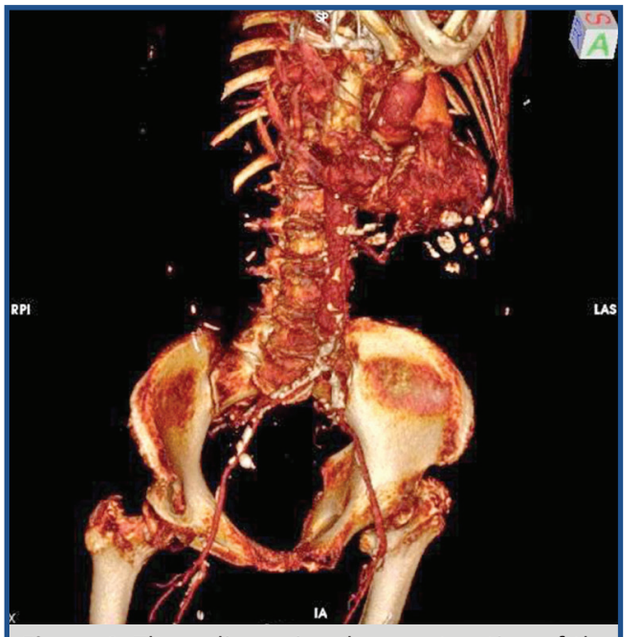
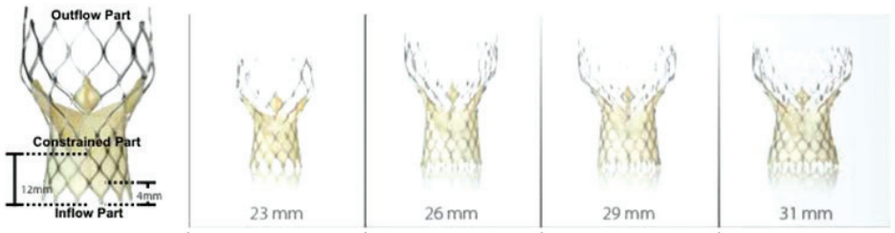


Figure 4. Three dimensional reconstruction of the aorto-ilio-femoral axis; diameter and calcifications can be analyzed using the transverse plane.

patients candidate to TAVI. It allows careful evaluation of the aortic valve apparatus: aortic valve morphology diameter and perimeter, calcification burden, annulus, left ventricular outflow tract, sinus of Vasalva height and length, coronary ostia take off (Figure 2 and 3). This allows a correct sizing and the selection of the better prosthesis. Angio CT-scan of aorto-iliac and femoral arteries is important for choosing the optimal vascular access (figure 4), i.e, femoral route or alternative, such as the trans-axillary/subclavian access, which consisted in a surgical exposure of the proximal part of the transaxillary artery, showing clear advantage in hostile vessel anatomies[20-23]; the trans-apical with surgical exposure of the left ventricular apex using customized introducer, balloon and device; and the last described approach, which is the trans-aortic one, requiring surgical access of the ascending aorta. All these vascular routes showed to be safe in selected patients, with high procedural success and acceptable complication rate[24].

Once the patient is judged suitable for TAVI because all the clinical indication requirements (valvulopathy and surgical risk) have been satisfied and the aortic valve anatomy refereed suitable, it is necessary to evaluate the pre procedural clinical condition, ruling out any pulmonary or urine infections and hemocuagulative disorder, and assess lung, renal and hepatic function, in order to be ready to face promptly any complications secondary to comorbidities. A 24 hours ECG Holter monitoring is recommended to detect baseline rhythm disorders.



Outflow Part Diam.	34	40	43	45
Constrained Part Diam.	20	22	24	24
Inflow Part Diam.	23	26	29	31
Valve Height	45	55	53	52

Figure 5. The e CoreValve® family (Medtronic, Minneapolis, MN, USA). The prosthesis frame consists of three distinct regions: the lower inflow portion that has high radial strength for facilitating device anchoring; the constrained middle portion, which incorporates the valve leaflets and has the smallest diameter to avoid coronary ostial jailing and the outflow portion serving to orient the frame to the direction of blood flow in the ascending aorta .

A standardized pre-medication regimen consists of aspirin 100 mg once daily and loading dose of Clopidogrel 300 mg on the day before the procedure. Prophylactic antibiotic therapy is administered 24 hours before TAVI. Moreover, two units of concentrated red cells are reserved in consideration for the possibility of haemorrhagic complications.

Device and procedure description

The third generation 18 French CoreValve Revalving® System for TAVI (Medtronic *Inc.* MN, USA) is a self expandable nitinol frame with a biological valve made of porcine pericardium available in four sizes (figure 5): the 23 mm CoreValve® Evolut™ prosthesis is indicated for annulus 18-20 mm and perimeter 56,5-62,8 mm; the 26 mm prosthesis is indicated for annulus 21-23 mm, perimeter 62,8-72,2 mm; the 29 mm valve is indicated in annulus 24-27 mm, perimeter 72,2-84,8 mm; the 31 mm valve is indicated in annulus 27-29 mm and perimeter 81,6-91,1 mm. The prosthesis frame is comprised of three distinct regions that interact with the aortic root at different levels (figure 5). The lower inflow portion has high radial strength for facilitating device anchoring. The constrained middle portion incorporates the valve leaflets and has the smallest diameter to avoid coronary ostial jailing. The outflow portion serves to orient the frame to the direction of blood flow in the ascending aorta.

The procedures are performed with surgical back up, under fluoroscopic guidance, and in a standard cardiac catheterization laboratory.

The anaesthesiological management is chosen basing on the patient condition. In our center analgo sedation without endo-tracheal intubation is the preferred approach for the following reasons: more stable hemodynamic of the patient, spontaneous breathing, shorten in-ICU stay and reduction in post procedural pulmonary disorders. Further extubation time in case of general anaesthesia and traditional endo-tracheal intubation is an unpredictable factor, especially for elderly people who have lung diseases and other severe comorbidities. General anaesthesia is the preferential way during transaortic or transapical access, or other accesses when transesophageal ehcoacardiographic monitoring is required. For adequate patient monitoring during the intervention it is always recommended a central venous catheter (CVC) placed in the right jugular vein or left subclavian vein in all patients for drug delivery, fluid administration and monitoring of central venous pressure (CVP). A radial artery cannula for invasive pressure measurement is usually placed. The worst femoral access is chosen for the 5 Fr diagnostic pig tail catheter. A temporary pacing is positioned in the right ventricular (RV) apex through a venous access.

Vascular accesses preparation

Vascular accesses can be obtained in percutaneous fashion for the transfemoral, when preclosure percutaneous systems are available like Prostar XL 10 F (Abbott Vascular Devices, Redwood City, C) or with surgical exposure in all the others. There are advantages and disadvantages for both approaches. Surgical exposure is recommended for complex vascular anatomy and for transaxillary artery, increasing the procedural time and the in-hospital stay but reducing vascular complications.

The femoral artery for insertion of the 18Fr introducer (selected after reviewing CT images) is accessed under angiographic guidance. The principal points are the following:

1) A 9Fr introducer is inserted into the common femoral artery.

2) After confirming access, the 9Fr introducer is removed over a 0.035” J-wire and a 10Fr-Prostar –XL device is inserted and all four sutures are harvested in a Preclose fashion.

3) The 9Fr introducer is reinserted and a super-stiff Amplatz wire (SSA-1) is placed in the aorta.

4) An 18Fr introducer is then advanced under fluoroscopy over the SSA-1 wire above the level of the aortic bifurcation.

If surgical exposure of femoral artery is performed, after femoral artery exposure and the 9 F introducer insertion only the points 3 and 4 are performed.

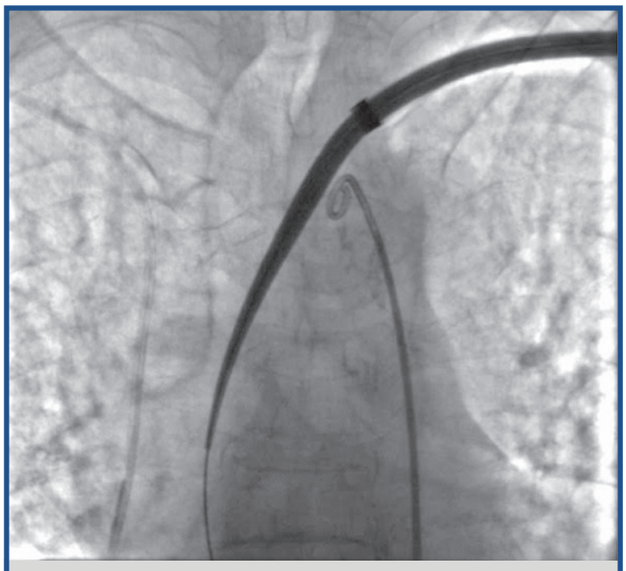


Figure 6. The 18 F introducer is inserted from the distal part of the left axillary artery. The tip of the introducer with radipaque marker is advanced at least 10 mm in the aortic arch.

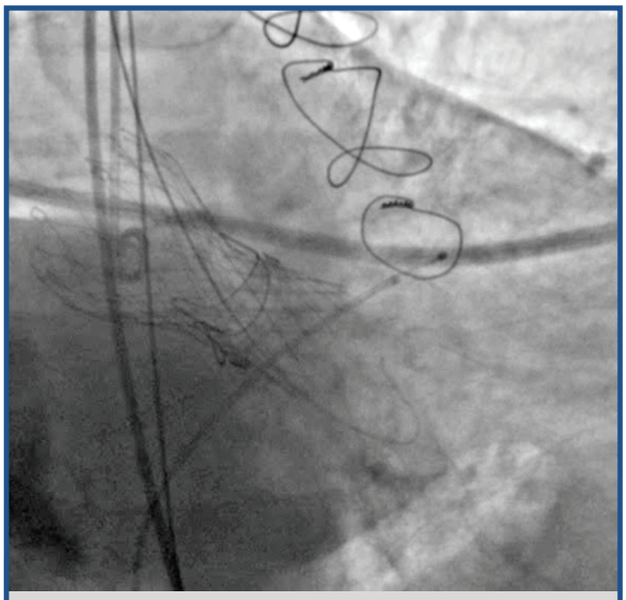


Figure 7. Left anterior oblique projection. A 23 mm CoreValve is positioned within a Edward Carpentier 21 mm surgical bioprosthetic valve.

When femoral access with the 18Fr introducer is contraindicated, the left distal axillary artery with surgical exposure can be used as alternative route[25]. The left arm is fixed in a position of abduction and external rotation at 90° degrees. A skin and deep-tissue incision is then made along a line that follows the course of the artery originating from the apex of the axilla and projecting itself into the crook of the elbow. The axillary artery is exposed upstream and downstream to the puncture site. After isolation, the artery is accessed with a18 G needle and a 7Fr introducer is advanced over a 0.035" 145 cm j-tip standard guide wire. A 5Fr pigtail catheter is positioned in the ascending aorta above the aortic valve plane and the standard guide wire is exchanged for SSA-1 wire (Boston Scientific Corp). A small transverse nick is made in artery wall and the 18-Fr introducer is advanced till the distal radiopaque marker is protruding at least 10 mm in the aortic arch (figure 6). The proximal part of the introducer is secured to the skin with a 00 silk suture .

Implantation technique

After crossing the native aortic valve with a standard diagnostic Amplatz left (AL-1) catheter and straight tip wire, a SSA-1 wire with a hand shaped loop at the end is placed in the left ventricular apex in stable position using the right anterior oblique projection. A pre-implantation balloon aortc valvuloplasty is routinely performed under rapid RV pacing with an undersized balloon for preparing the native annulus except in pure aortic regurgitation or degenerated aortic bioprosthesis (figure 7).

The CoreValve implantation is performed as follow: a 5 fr diagnostic pigtail catheter is positioned in the non-coronary cusp as a marker for the annular plane and for contrast injections during the valve release. The image intensifier is positioned in the optimal left anterior oblique (LAO) projection for aligning all three coronary cusps in a straight line. The delivery catheter system (DCS) is positioned such that one horizontal markers of the device is positioned below the level of the pigtail catheter and the release is initiated under fluoroscopic and angiographic guidance with repeated small contrast injections (10 cc to 10 cc/sec at 900 psi) through the pigtail catheter. The DCS frame must be positioned 4 to 6 mm below the annular plane prior to initiating release of the valve frame; the release of the valve must be performed very slowly making small adjustments for compensating undesired movement; he DCS is maintained in as central a position as possible in the aortic root, After the prosthesis is released completely, the release hooks of the device are carefully observed to ensure their detachment from the DCS in LAO and right anterior oblique projection projections.

Post deployment, hemodynamic measurements and ascending aortogram must be performed to assess for presence and severity of para-prosthetic regurgitation (PPR).

How to assess a paravalvular leak

When a paravalvular leak is observed after implantation the operator should accurately evaluate the severity of the PPR, and understand the underlying mechanis . The severity of the regurgitation must be assessed using hemodynamic measurements, angiographic and echocardiographic evaluation.

The simultaneous recording of aortic pressure and left ventricular (LV) pressure gives a lot of information. When the diastolic aortic pressure is below 40 mmHg and the LV end-diastolic pressure is higher than baseline the aortic regurgitation is likely to be severe and must be corrected (figure 8). The aortography should be performed with adequate volume and rate of contrast in-

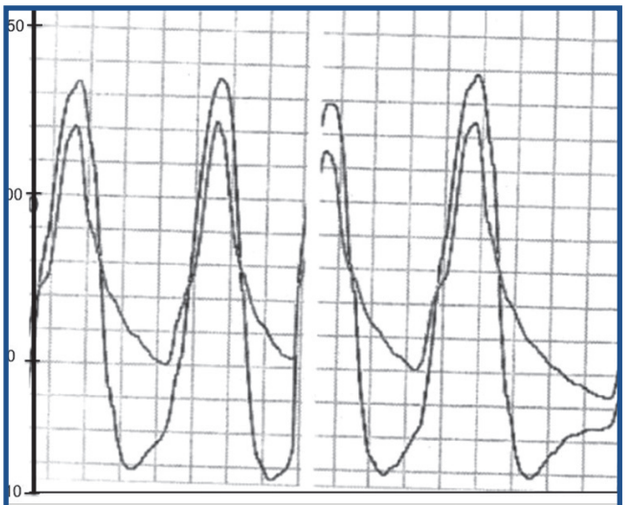


Figure 8. Hemodinamic assesssment of severe aortic regurgitation by simultaneous measurement of aortic and left ventricular pressures.

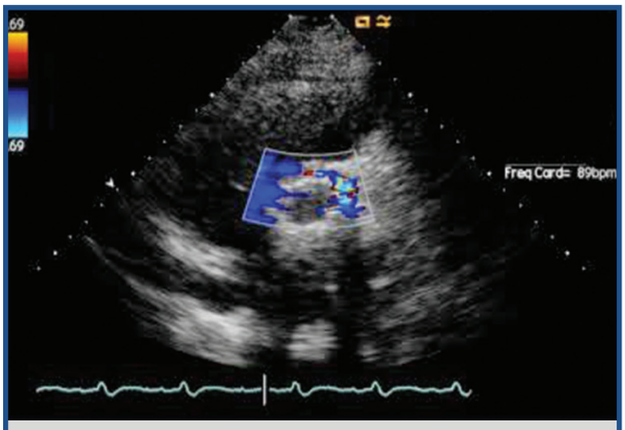


Figure 9. Transthoracic echocardiogram short axis view showing para-prosthetic leak extended from 12 to 4 o'clock.

jection in two orthogonal views in order to quantify the severity of regurgitation, identify the location and mechanism of the leak, understanding if it occurred for incomplete prosthesis expansion or incomplete apposition. In this case the inlet portion of the valve is few millimeter far away from the calcified annulus only under one cups for the presence of a calcification, or in multiple locations because undersized valve.

If there is a low valve malposition the mechanism of leak is a inadequate sealing of the inlet portion of the CoreValve, so the blood returns in the ventricle passing through the struts above the upper part of the pericardium skirt, When there is an high valve malposition we can have severe regurgitation and /or coronary ostia obstruction by the inlet part of the prosthesis.

The trans-thoracic echocardiography is a useful diagnostic tool, when the acoustic window is optimal, and using the three main views (parasternal long axis, parasternal short axis and the apical five chamber), it is possible to understand the position and extension of the leak, the severity of regurgitation and the impairment of the LV (figure 9).

If there is a under expansion of the valve, or malapposition of one side of the valve, balloon post dilatation is recommended during a careful right ventricular pacing for reducing the left ventricular systolic pressure in order to obtain a stable balloon position. If the valve is too high, the first maneuver is to snare the valve from one of the two hooks and pull the valve in the ascending aorta, because the danger of coronary flow obstruction. Then place a second valve. The so called „valve- on-valve", does not impair the device function . If the valve is too low try to pull the valve of few mm using a snare with a „pull and stop" technique: the snare is inserted from one of the femoral artery, and one of the two hooks is catched and start pulling till when the beating heart is felt ,the stop and maintain the position, wait few minutes and then start again[26]. Sometimes the femoral approach is not uncomfortable for snaring the valve, in this case from an artery access from the left arm (radial or brachial) for obtaining a better catheter snare direction of traction[27]. If this maneuver is ineffective, the „valve-in-valve" technique is the second option, placing a second valve within the first[28,29].

Once the prosthesis is successfully deployed, removal of vascular catheters is carried out in the catheterization laboratory. The temporary pacemaker electrode placed into the right ventricle through a femoral vein is maintained for 24-48 hours.

Post procedural Intensive care management

The post-operative care is challenging because of the incidence of procedural and post procedural life threatening complications related to the invasiveness of TAVI and to the abrupt hemodynamic changes occurring after the sudden relief of valvular obstruction in patients with a chronically low cardiac output state[30].

After the procedure all patients are routinely transferred to the ICU. During the first 48 hours, vital parameters are continuously monitored by a nurse. Close attention has to be given to rhythm and atrio-ventricular conduction disturbances, systemic blood pressure and fluid balance, monitoring diuresis and adjusting intravenous fluid administration in order to maintain CVP between 5 to 10 mmHg. Oxygen saturation values are obtained from transcutaneous pulse oximetry, with arterial blood gas test when necessary

Assessment of cardiologic symptoms, such as palpitations, chest pain, fatigue and shortness of breath, and examination of mental status, including consciousness, orientation and memory, require a careful observation of patients for the early detection of signs of acute heart failure or neurological deficit.

Vascular accesses and peripheral pulses are monitored for hematoma, pseudo-aneurysm or acute thrombosis. When necessary a peripheral echo-Doppler is performed.

To prevent infections, stringent cleaning of vascular accesses and care of urinary catheter are daily advised. If signs of systemic infection are present, blood and/or urinary cultures are ordered.

Laboratory tests are performed daily and consisted in: blood routine count for detecting signs of occult

bleeding, infection, dual antiplatelet therapy intolerance or heparin induced thrombocytopenia and for the assessment of renal function to diagnose acute kidney insufficiency (AKI) defined as a decrease of > 25% in eGFR at 48 hours following the procedure or the need of haemodialysis during hospitalization [31-35]. The degree of AKI is further classified as: (i) mild (> 25% decrease in eGFR); (ii) moderate (50-75% decrease in eGFR), and (iii) severe (>75% decrease in eGFR).(36)

Other routine laboratory test included: electrolytes serum concentrations, liver and muscular enzymes and clotting parameters.

A trans-thoracic echocardiogram is planned 6 hours after TAVI and then every 24 hours, to assess optimal position of the prosthesis, trans-prosthetic gradient, paravalvular leak or aortic regurgitation, mitral valve and left ventricular function, systolic pulmonary arterial pressure and pericardial effusion.

Standard medical therapy include low molecular weight heparin until ambulation, appropriate antibiotic therapy for three days, acetylsalicylic acid (100mg) and Clopidogrel (75mg) daily; inotropic support, antihypertensive and diuretic therapy if needed.

Early patient ambulation, within 24/48 hours, is encouraged to prevent complications, such as muscle atrophy, constipation, decubitus ulcers, thrombo-phlebitis and to reduce length of hospital-stay. Patients should undergo physical rehabilitation just after mobilization and pulmonary rehabilitation in patients with pulmonary diseases expecially in case of intra-procedural endo-tracheal intubation.

Renal failure. Chronic kidney disease is a predisposing factor for post-procedural AKI (30-35). However, patients with normal baseline renal function can develop post-procedural AKI despite a low volume of contrast medium used. These patients can have an intense polyuric phase soon after TAVI, followed by an oliguric status. The mechanism can be the sudden decrease in heart filling pressures matched to a significant increase in cardiac output and kidney perfusion just after valve implantation. This polyuria is followed by intravascular volume reduction, confirmed by a marked drop in CVP, which led to a prerenal acute renal failure. Therefore, a careful monitoring of the fluid balance with continuous CVP measurement and intravenous volume repletion to correct fluid loss is mandatory to lower the rate of AKI. When pre-renal acute renal failure occurs protocol for fluid replacement therapy tailored to maintain the CVP value between 5 to 10 mmHg.

Diuretics have to be administered only in those patients with low left ventricular ejection fraction, severe LV diastolic dysfunction, coexistence of severe mitral regurgitation and RV dysfunction with severe pulmonary hypertension; also patients with persistent oliguria despite optimization of intravascular volumes and cardiopulmonary hemodynamics could benefit from diuretic drugs.

Vascular complications. Femoral artery pseudoaneurism (FAP) is the most common vascular complication after TAVI. Physical examination of vascular accesses sites and peripheral pulses have to be systematically performed every 3 hours looking for bleeding, pulsatile hematoma or acute signs of limb ischemia. Color Doppler ultrasound scanning can be performed in cases of groin pulsatile masses to confirm or to exclude the presence of FAP. Manual compression repair under ultrasound monitoring significantly reduce the need for surgical repair of FAP, leading to early patient ambulation and short hospital stay. Surgical vascular intervention is the preferred as first-line treatment in patients with signs of acute haemodynamic compromission or if manual compression failed (30,37).

Conduction Disturbances. These frequently consist in Left Bundle Branch Block (LBBB), or advanced or complete atrio-ventricular block (AVB) within the first 24 hours of TAVI. Complete AVB is a potential acute and late complication of TAVI. It is hypothesized that continued prosthesis expansion can cause a mechanical trauma to the conduction system, particularly in patients with calcified aortic annulus, worsening pre-existing conduction defects or generating new ones. The atrioventricular node is in fact in close proximity to the subaortic region and membranous septum of left ventricle outflow tract. Therefore proper positioning of the prosthesis within the left ventricular outflow tract may limit risk of conduction abnormalities and potentially the need for pacing [39]. It is now recommended to position the proximal end of the valve frame < 6 mm from the lower edge of the noncoronary cusp. Permanent pacemaker implantation is recommended as early as possible.

Cerebrovascular accident is a rare complication, ranging from 2 to 4 % (7-12, 40,41) , they occur intraprocedurally, and mostly are minor stroke. Severe aortic arch calcificationscan be a source of increased embolization during wire manipulation, catheter exchanges in aorta and when the device is retrieved and then repositioned. In this case the flared distal part of the prosthesis can scratched the atheromatous aortic wall resulting in cerebral micro-embolization.

Thrombocytopaenia usually is caused by anticoagulant therapy, as confirmed by the rapid and spontaneous resolution after heparin withdrawal (42). The use of fondaparinux as thromboembolic prophylaxis is attractive and we recently introduced in postoperative protocol as routine anticoagulation . All these data emphasize the importance of a strict platelet count control.

Currently, the optimal antithrombotic prophylaxis remains embroiled in controversies (43,44). About Corevalve prosthesis, it is only speculated that before the process of endothelization, the risk of thrombosis induced by the prosthesis is high and that dual antiplateled therapy should be advocated for at least the first three months after the implantation. However, taking into account that there are no reports on embolic events after TAVI, the perceived high risk of developing valve thrombosis and systemic thromboembolism may not be real. Our experience shows that the use of dual antiplatelet therapy is to some extent “empirical” and that in selected patients, without unstable coronary artery disease, the long-life use of aspirin is effective, more economic and possibly better tolerated by pa-

tients. After TAVI dual antiplatelet therapy with aspirin and clopidogrel for three up to six months is currently recommended, but there is no scientific evidence supporting this strategy (43). Therefore antithrombotic therapy with aspirin alone can be offered in those patients at high risk of major bleeding

Conclusions

TAVI is a novel technique for the interventional cardiologist, which requires a careful assessment of the clinical conditions of candidate patients in order to have a safe and effective procedure. The post-operative care needs a level of attention higher than other percutaneous interventions, due to the high-risk characteristics of this patient population such as advanced in age, frailty and comorbidities. The potential complications are known, but a standardized monitoring and management protocol and a specific training of caregivers would be useful for the early recognition and treatment of complications, which will result in a more favourable outcome.

References

1. Zajarias A, Cribier AG. Outcomes and safety of percutaneous aortic valve replacement. J Am Coll Cardiol 2009;53:1829-1836.
2. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, Devarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, Delarochellière R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. Transcatheter Aortic Valve Implantation for the Treatment of Severe Symptomatic Aortic Stenosis in Patients at Very High or Prohibitive Surgical Risk Acute and Late Outcomes of the Multicenter Canadian Experience. J Am Coll Cardiol 2010.
3. Piazza N, Grube E, Gerckens U, Den Heijer P, Linke A Luha O, Ramondo A.B., Ussia GP, Wenaweser P, Windecker S, Laborde J.C.,De Jaegere P, Serruys P.W: on the behalf of the clinical centres who actively participated in the registry. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) CoreValve ReValving System: results from the multicentre, expanded\evaluation registry 1-year following CE mark approval. EuroInterv 2008; 4: 242-249.
4. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–1607.
5. Authors/Task Force Members, Vahanian A, Alfieri O, et al. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal 2012;33:2451–2496.
6. Vahanian A, Alfieri O, Al-Attar N , Antunes M, Bax J, Cormier B, Cribier A, De Jaegere P, Fournial G, Kappetein AP, Kovac J, Ludgate S, Maisano F, Moat N, Mohr F, Nataf P, Pièrard L, Pomar JL, Schofer J, Tornos P, Tuzcu M, van Hout B, Von Segesser LK, Walther T, Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J 2008; 11: 1463-1470.
7. Tamburino C, Capodanno D, Mulè M, Scarabelli M, Cammalleri V, Barbanti M, Calafiore A, Ussia GP. Procedural success and 30-day clinical outcomes after percutaneous aortic valve replacement using current third-generation self-expanding CoreValve prosthesis.J Invasive Cardiol 2009 Mar;21(3):93-98.
8. Ussia GP, Barbanti M, Petronio AS, Tarantini G, Ettori F, Colombo A, Violini R, Ramondo A, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, De Carlo M, Napodano M, Fiorina C, De Marco F, Antoniucci D, de Cillis E, Capodanno D, Tamburino C; CoreValve Italian Registry Investigators Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. Eur Heart J 2012;33:969-76.
9. Zahn R, Gerckens U, Linke A, Sievert H, Kahlert P, Hambrecht R, Sack S, Abdel-Wahab M, Hoffmann E, Schiele R, Schneider S, Senges J; German Transcatheter Aortic Valve Interventions-Registry Investigators. Predictors of one-year mortality after transcatheter aortic valve implantation for severe symptomatic aortic stenosis. Am J Cardiol 2013;112:272-9.
10. Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, Thomas M, Kovac J, Spyt T, MacCarthy PA, Wendler O, Hildick-Smith D, Davies SW, Trivedi U, Blackman DJ, Levy RD, Brecker SJ, Baumbach A, Daniel T, Gray H, Mullen MJ. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol 2011;58:2130-8.
11. Gilard M1, Eltchaninoff H, Iung B, Donzeau-Gouge P, Chevreul K, Fajadet J, Leprince P, Leguerrier A, Lievre M, Prat A, Teiger E, Lefevre T, Himbert D, Tchetche D, Carrié D, Albat B, Cribier A, Rioufol G, Sudre A, Blanchard D, Collet F, Dos Santos P, Meneveau N, Tirouvanziam A, Caussin C, Guyon P, Boschat J, Le Breton H, Collart F, Houel R, Delpine S, Souteyrand G, Favereau X, Ohlmann P, Doisy V, Grollier G, Gommeaux A, Claudel JP, Bourlon F, Bertrand B, Van Belle E, Laskar M; FRANCE 2 Investigators. Registry of transcatheter aortic-valve implantation in high-risk patients. N Engl J Med 2012;366:1705-15.
12. Toggweiler S, Humphries KH, Lee M, Binder RK, Moss RR, Freeman M, Ye J, Cheung A, Wood DA, Webb JG. 5-year outcome after transcatheter aortic valve implantation. J Am Coll Cardiol. 2013 Jan 29;61(4):413-9.
13. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, Fontana GP, Dewey TM, Thourani VH, Pichard AD, Fischbein M, Szeto WY, Lim S, Greason KL, Teirstein PS, Malaisrie SC, Douglas PS, Hahn RT, Whisenant B, Zajarias A, Wang D, Akin JJ, Anderson WN, Leon MB; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686-95.
14. Roques F, Nashef SA, Michel P, Gauducheau E, de Vincentiis C,Baudet E, Cortina J, David M, Faichney A, Gabrielle F, Gams E, Harjula A, Jones MT, Pintor PP, Salamon R, Thulin L. Risk factors and outcome in European cardiac surgery: analysis of the EuroSCORE multinational database of 19030 patients. Eur J Cardiothorac Surg 1999;15:816-822.
15. . Nashef SAM, Roques F, Sharples LD, et al. EuroSCORE II. Eur J Cardiothorac Surg 2012;41:734–745.
16. Dewey T. M, Brown D, Ryan W.H, Herbert M.A, Prince S. L, and Mack M. J, Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. J Thorac Cardiovasc Surg 2008;135:180-7
17. Wendt D, Osswald B. R, Kayser K, Thielmann M, Tossios P, Massoudy P, Kamler M, and Jakob H. Society of Thoracic Surgeons Score Is Superior to the EuroSCORE Determining Mortality in High Risk Patients Undergoing Isolated Aortic Valve Replacement. Ann Thorac Surg 2009;88:468 –75.
18. Vassiliades TA Jr, Block PC, Cohn LH, Adams DH, Borer JS, Feldman T, Holmes DR, Laskey WK, Lytle BW, Mack MJ, Williams DO; Society of Thoracic Surgeons (STS); American Association for Thoracic Surgery (AATS); Society for Cardiovascular Angiography and Interventions (SCAI); American College of Cardiology Foundation (ACCF); American Heart Association (AHA). The clinical development of percutaneous heart valve technology: a position statement of the Society of Thoracic Surgeons (STS), the American Association for Thoracic Surgery (AATS) and the Society for Cardiovascular Angiography and Interventions (SCAI). Ann Thorac Surg 2005; 79:1812–1818.
19. Kappetein AP, Head SJ, Généreux P, Piazza N, van Mieghem NM, Blackstone EH, Brott TG, Cohen DJ, Cutlip DE, van Es GA, Hahn RT, Kirtane AJ, Krucoff MW, Kodali S, Mack MJ, Mehran R, Rodés-Cabau J, Vranckx P, Webb JG, Windecker S, Serruys PW, Leon MB. Updated standardized endpoint definitions for transcatheter aor-

tic valve implantation: the Valve Academic Research Consortium-2 consensus document (VARC-2). Eur Heart J 2012;33:2403-18.
20. Buellesfeld L, Stortecky S, Kalesan B, et al. Aortic root dimensions among patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. JACC Cardiovasc Interv 2013;6:72–83.
21. Walther T, Simon P, Dewey T, et al. Transapical minimally invasive aortic valve implantation: multicenter experience. Circulation 2007; 116:I240.
22. Petronio AS, De Carlo M, Bedogni F, Marzocchi A, Klugmann S, et al. Safety and efficacy of the subclavian approach for transcatheter aortic valve implantation with the CoreValve revalving system. Circulation Cardiovasc Interv 2010;3:359–366.
23. Modine T, Sudre A, Collet F, Delhaye C, Lemesles G, Fayad G, Koussa M. Transcutaneous aortic valve implantation using the axillary/subclavian access with patent left internal thoracic artery to left anterior descending artery: feasibility and early clinical outcomes. J Thorac Cardiovasc Surg 2012;144:1416-20.
24. Latsios G, Gerckens U, Grube E. Transaortic transcatheter aortic valve implantation: a novel approach for the truly no-access option patients. Catheter Cardiovasc Interv 2010;75:1129–1136.
25. Ussia GP, Cammalleri V, Ascoli Marchetti A, Sarkar K, De Vico P, Muscoli S, Sergi D, Marchei M, Ippoliti A, Romeo F. Transcatheter aortic valve implantation through distal axillary artery: novel option for vascular access. J Cardiovasc Med (Hagerstown) 2014. Doi: 10.2459/JCM.0000000000000063
26. Ussia G., Barbanti M, Sarkar K, Aruta P, Scarabelli M, Cammalleri V, Imme S, Pistritto Am, Gulino S, Mule M, Deste W, Cannata S, Tamburino C (2012). Transcatheter Aortic Bioprosthesis Dislocation: Technical Aspects And Midterm Follow-Up. Eurointervention, Vol. 7; P. 1285-1292.
27. Ussia GP, Barbanti M, Immè S, Scarabelli M, Mulè M, Cammalleri V, Aruta P, Pistritto AM, Capodanno D, Deste W, Di Pasqua MC, Tamburino C. Management of implant failure during transcatheter aortic valve implantation. Catheter Cardiovasc Interv. 2010;76:440-9.
28. Ussia GP, Barbanti M, Ramondo A, Petronio AS, Ettori F, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, Napodano M, Tamburino C. The valve-in-valve technique for treatment of aortic bioprosthesis malposition an analysis of incidence and 1-year clinical outcomes from the italian CoreValve registry. J Am Coll Cardiol 2011;57:1062-8.
29. Ussia GP, Mulè M, Tamburino C. The valve-in-valve technique: transcatheter treatment of aortic bioprothesis malposition. Catheter Cardiovasc Interv 2009;73:713-6.
30. Ussia G., Scarabelli M, Mule M, Barbanti M, Cammalleri V, Imme S, Aruta P, Pistritto Am, Carbonaro A, Deste W, Sciuto P, Licciardello G, Calvi V, Tamburino C. Postprocedural Management Of Patients After Transcatheter Aortic Valve Implantation Proicedure With Self Expanding Bioprostehsis. Catheter Cardiovasc Interv. 2010 Nov 1;76(5):757-66.
31. Tepel M, van der Giet M, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000 Jul 20;343(3):180-184.
32. Birck R, Kzossok S, Markowetz F, Schnulle P, Van der Woude FJ, Braun C. Acetylcysteine for prevention of contrast nephropathy: meta-analysis. Lancet 2003; 362: 598-603.
33. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, Marsch S, RoSkamm H. Prevention of contrast media-associated nephropathy; randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 2002; 162: 329-336.
34. Briguori C, Colombo A, Violante A, Balestrieri P, Manganelli F, Elia PP, Golia B, Lepore S, Riviezzo G, Scarpato P, Focaccio A, Librera M, Bonizzoni E, Ricciardelli B. Standard vs double dose of N-acetylcysteine to prevent contrast agent associated nephrotoxicity. European Heart Journal (2004) 25, 206-211.
35. Bagur R, Webb JG, Nietlispach F, Dumont E, De Larochelliere R, Doyle D, Masson JB, Gutierrez MJ, Clavel MA, Bertrand OF, Pibarot P, Rodes- Cabau J. Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement. Eur Heart J 2009.
36. Bellomo R, Kellum JA, Ronco C. Defining and classifying acute renal failure: from advocacy to consensus and validation of the RIFLE criteria. Intensive Care Med 2007; 33:409-413.
37. Fellmeth BD, Roberts AC, Bookstein JJ, et al. Postangiographic femoral artery injuries: nonsurgical repair with US-guided compression. Radiology 1991; 178:671-675.
38. Fraccaro C, Napodano M, Tarantini G, Gasparetto V, Gerosa G, Bianco R, Bonato R, Pittarello D, Isabella G, Iliceto S and Ramondo A. Expanding the Eligibility for Transcatheter Aortic Valve Implantation: The Trans-Subclavian Retrograde Approach Using the III Generation CoreValve Revalving System. J Am Coll Cardiol Intv 2009;2:828-833.
39. Piazza N, Onuma Y, Jesserun E, Kint PP, Maugenest AM, Anderson RH, de Jaegere PP, Serruys PW. Early and persistent intraventricular conduction abnormalities and requirements for pacemaking after percutaneous replacement of the aortic valve. JACC Cardiovasc Interv 2008;1:310-316.
40. Hynes BG, Rodés-Cabau J. Transcatheter aortic valve implantation and cerebrovascular events: the current state of the art. Ann N Y Acad Sci 2012 Apr;1254:151-63.
41. Tay EL1, Gurvitch R, Wijesinghe N, Nietlispach F, Wood D, Cheung A, Ye J, Lichtenstein SV, Carere R, Thompson C, Webb JG. A high-risk period for cerebrovascular events exists after transcatheter aortic valve implantation. JACC Cardiovasc Interv 2011;4:1290-7.
42. Shantsila E, Lip GYH and Chong BH. Heparin-Induced Thrombocytopenia Chest 2009;135;1651-1664.
43. Ussia G., Scarabelli M, Mule M, Barbanti M, Sarkar K, Cammalleri V, Imme S, Aruta P, Pistritto Am, Gulino S, Deste W, Capodanno D, Tamburino C (2011). Dual Antiplatelet Therapy Versus Aspirin Alone In Patients Undergoing Transcatheter Aortic Valve Implantation. Am J Cardiol 2012;108:1772-1776.
44. Lynch DR Jr, Dantzler D, Robbins M, Zhao D. Considerations in antithrombotic therapy among patients undergoing transcatheter aortic valve implantation. J Thromb Thrombolysis. 2013 May;35(4):476-82.

Srce i krvni sudovi 2014; 33(1): 21-26

Originalni rad

Balloon aortic valvuloplasty of severe aortic stenosis in the era of TAVR

P. Kogoj[1], T. Furlan[2], M. Bunc[1]

[1]Department of Cardiology, Division of Internal Medicine, University Medical Centre Ljubljana, Slovenia
[2]Department of Internal Medicine, General Hospital Jesenice, Slovenia

Abstract

Introduction. Balloon aortic valvuloplasty (BAV) is a percutaneous treatment option for aortic stenosis (AS). Because of early restenosis and poor long-term survival, it is used as a bridge to surgery (SAVR) or transcatheter aortic valve replacement (TAVR), in hemodinamically unstable patients or patients that require urgent non-cardiac surgery.

Aim. The aim of this study was to evaluate all the BAV procedures performed in our centre in 2010 and to report our experience with BAV as a potential bridge to definitive therapy or as a palliative treatment.

Methods. We retrospectively analyzed all the patients who underwent percutaneous treatment of aortic stenosis in our institution between January and December 2010. We stratified our cohort into 3 groups: BAV as a bridge to TAVR or SAVR, BAV as a final therapy and TAVR without prior BAV. We evaluated patient characteristics, echocardiographic data and peri-procedural complications in each cohort. Survival was evaluated using Kaplan-Meier analysis.

Results. We included 86 high risk symptomatic patients with mean age of 82.2 ± 5.0 years and mean logistic EuroSCORE of 19.2 ± 11.8 %. After BAV we observed a significant decrease in mean transvalvular gradient (from 43.8 ± 14.4 to 33.5 ± 12.3 mmHg; $p < 0.01$) and a significant increase in aortic valve area after BAV (from 0.6 ± 0.2 to 0.8 ± 0.3 cm^2; $p < 0.01$). Systolic pulmonary artery pressure, left ventricular ejection fraction and mitral regurgitation did not change significantly. Major intrahospital complications occurred in 5 patients (6.5 %), without any death related to the procedure. BAV as a bridge to TAVR had a better outcome compared with BAV alone.

Conclusion. BAV is a feasible and reasonably safe approach for temporary relief of symptoms, improvement of quality of life, decrease of surgical risk prior major non-cardiac surgery or as a bridge to surgical or transcatheter aortic valve implantation in severe aortic stenosis.

Introduction

Calcific stenosis of the aortic valve (AS) is the most common acquired valve disorder in the Western world[1]. Surgical aortic valve replacement (SAVR) is considered the treatment of choice in patients with symptomatic AS regardless of age[2, 3]. The surgical risk in elderly patients with multiple comorbidities may be high and the presence of concomitant coronary artery disease (CAD) with the need for additional coronary artery bypass may duplicate the risk[4–6]. Balloon aortic valvuloplasty (BAV) was introduced in 1986 as the first less invasive percutaneous treatment option of symptomatic AS[7]. Unfortunately, early restenosis of the dilated valve with symptoms recurrence and poor long-term survival limits the use of this procedure[8–12]. Today BAV may be considered as a bridge to surgery or percutaneous aortic valve replacement (TAVR) in haemodynamic unstable patients or patients that require urgent major non-cardiac surgery. Balloon valvuloplasty may also be considered as a palliative measure in selected individual cases when surgery is contraindicated because of severe comorbidities and when TAVR is not an option[13].

Percutaneous aortic valve treatment program started in our medical centre in 2008 as a part of preparation for TAVR program. BAV was not frequently used in our centre before. Since 2008 we performed over 330 BAV procedures and 110 TAVR implantations. The present study evaluated all the BAV procedures we performed in 2010 and reports our experience with BAV in symptomatic high risk patients with severe aortic stenosis, as a potential bridge to definitive therapy or as a palliative treatment.

Methods

Patient population and selection

We retrospectively analyzed all the patients who underwent percutaneous treatment of aortic stenosis in our institution between January and December 2010. We stratified our cohort into 3 groups according to the

Correspondence to Matjaž Bunc, MD PhD, Professor of internal medicine and pathophysiology, University Medical Center Ljubljana, Zaloška c. 007, 1000 Ljubljana, Slovenia, mbuncek@yahoo.com

final treatment: BAV as a bridge to TAVR or SAVR, BAV as a final therapy (including repeated BAV) and TAVR without prior BAV.

Criteria for BAV and/or TAVR included:

– symptomatic aortic stenosis confirmed by transthoracic echocardiography with aortic valve area < 1 cm^2 (< 0.6 cm^2/m^2),

– operative risk estimated by logistic EuroSCORE (European System of Cardiac Operative Risk Evaluation) > 15 %,

– contra-indication for surgery because of comorbid conditions; assessed and agreed to by both an independent cardiologist and a cardiovascular surgeon.

Criteria for BAV as a bridge to TAVR or SAVR included:

– hemodynamic unstable patient,

– prior urgent major non-cardiac surgery (for example patients with carcinoma),

– mitral regurgitation (MR) > 2+,

– pulmonary hypertension due to combination of COPB and left ventricular failure.

Echocardiographic data

The screening before and after the percutaneous procedure included transthoracic echocardiography (TTE) recording of aortic stenosis severity, aortic valve regurgitation, left ventricular function, additional mitral regurgitation and pulmonary artery systolic pressure.

BAV procedure

The procedures were performed in our cardiac catheterisation laboratory in local anesthesia. Patients selected for BAV underwent diagnostic right and left cardiac catheterization. In case of coronary artery disease an angioplasty was performed before BAV in the same intervention. Heparin (70UI/kg) was administered after 10F sheath insertion in the femoral artery and pig tail through 5F sheet in radial artery. Aortic valve was crossed by LA1 catheter (Cordis) and J wire. J.wire was substituted for supportive Amplatz stiff wire (Abbott). Via percutaneous trans-femoral approach a balloon catheter (Zelos, OptiMed, 18-25 mm x 4.0 cm) was introduced and positioned across the stenotic aortic valve. We used undersized dilatation balloons according to TTE annulus diameter. Aortic valvuloplasty was performed with balloon inflation (25-30 ml, burst rate 4 ATM). Selection of the balloon inflation size was based on the combination of transthoracic echocardiography, baseline aortography, and alignment of the balloon to aortic annulus during valvuloplasty balloon expansion. To stabilize the balloon position across the valve, rapid ventricular pacing (180-220 beats/min) was done during each inflation using temporary pacemaker electrode inserted in right ventricle through femoral vein. Before and after the valvuloplasty peak to peak pressure gradient was measure with pigtail catheters into aorta and left ventricle. The goal of the procedure was a reduction of the gradient by at least 50% and if necessary, the balloon inflation was repeated. In case of first BAV balloon under-sizing the second BAV was performed with the next, bigger sized balloon. Hemostasis was performed with vascular closure devices Proglide (Abbott vascular) or with direct manual compression of radial and femoral arterial puncture site ad once and after 3-4 hours, respectively.

TAVR procedure

The selection of TAVR candidates was done according to Edwards recommendations. All the patients were refused for classic AVR. Indication for TAVR was also conditioned by TAV availability. We used Edwards-Sapien devices. Sizing was done by combination of CTA and TEE. Implantations were performed in coronary cathlab in sterile regimen. TAVI team members (anaesthetist, cardiovascular surgeon, interventional cardiologists, ECHO specialists) participated in the patients selection. Patients were operated in general anesthesia. Both trans-apical and trans-femoral TAVR approaches were utilized.

Data collection and follow up

Baseline clinical data were retrospectively collected from the medical records. Logistic EuroSCORE was calculated for all patients based on baseline variables before the procedure. All clinically relevant baseline and follow-up variables as well as peri-procedural complication were prospectively entered into a dedicated database. In-hospital follow-up consisted of vital parameters, complete blood count and assessment of renal function, review of arterial puncture site and TTE within few days after BAV. Clinical and echocardiographic follow up was planned at 3 to 6 months after BAV and obtained from chart review.

Major peri-procedural adverse events were defined as peri-procedural death from any cause, myocardial infarction, severe acute aortic regurgitation, stroke, cardiac tamponade, cardiogenic shock, aortic dissection, major vascular complications, urgent or emergency conversion to surgery or permanent pacemaker requirement. Acute renal impairment, myocardial infarction, stroke, vascular complications and major bleeding were defined according to the Valve Academic Research Consortium proposed criteria (VARC)[14].

Statistical analysis

Qualitative variables were expressed as percentages and quantitative variables were expressed as mean ± standard deviation. Comparison of continuous variables was performed with the analysis of variance and Student's paired t-test, as appropriate. The $\chi 2$ test was used to compare qualitative variables. Survival rates were presented as Kaplan-Meier curves, and the log-rank test was used for comparison. Differences were considered statistically significant at $P < 0.05$. All data were processed using the Statistical Package for Social Sciences, version 17.0 (SPSS, Inc., Chicago, Illinois).

Results

The cohort included 86 consecutive patients who underwent percutaneous treatment of severe aortic stenosis in 2010 in our institution. BAV was performed in 77 patients (89.5 %), followed by TAVR in 19 patients (22.1

%) and SAVR in one patient (1.2 %). Nine patients (10.5 %) underwent TAVR without previous BAV procedure.

Baseline characteristics

The baseline characteristics of all patients are displayed in the Table 1. They all had symptomatic severe aortic stenosis with mean AVA of 0.6 ± 0.2 cm^2 and were at high risk for surgical valve replacement. All the patients were older than 80 years with the mean age of 82.2 ± 5.0 years, mean logistic EuroSCORE of 19.2 ± 11.8 and 54 (62.8 %) of them were presenting in New Your Heart Association (NYHA) class III/IV. Common comorbidities included hypertension (72.1 %), coronary artery disease (41.9 %) with previous coronary artery bypass grafting (14 %), chronic kidney disease (34.9 %), chronic obstructive pulmonary disease (26.7 %) and diabetes (25.6 %).

Indications for BAV

Table 1. Baseline characteristics of the overall population.

Variables	Overall population (n = 86)
Age, y	82.2 ± 5.0
Men, n (%)	28 (32.6)
Logisitic EuroSCORE	19.2 ± 11.8
Cardiogenic shock, n (%)	1 (1.2)
NYHA III and IV, n (%)	54 (62.8)
Diabetes, n (%)	22(25.6)
Hypertension, n (%)	62 (72.1)
Hyperlipidemia, n (%)	12 (14.0)
Coronary artery disease, n (%) (stenosis more than 70%)	36 (41.9)
Chronic obstructive pulmonary disease, n (%)	23 (26.7)
Chronic renal failure, n (%)	30 (34.9)
Prior CVI, n (%)	14 (16.3)
Atrial fibrillation, n (%)	43 (50)
Peripheral artery disease, n (%)	9 (10.5)
Prior coronary artery bypass grafting, n (%)	12 (14.0)
Prior percutaneous coronary intervention, n (%)	17 (19.8)
Prior myocardial infarction, n (%)	6 (7.0)
Neoplasma, n (%)	16 (18.6)
Porcelain aorta, n (%)	1 (1.2)
Mean aortic gradient, mm Hg	44.2 ± 13.7
Baseline AVA, cm^2	0.6 ± 0.2
AR grade	1-2/4
LVEF, %	52.0 ± 14.4
BAV and PCI as a single procedure	14 (16.3)
BAV prior non-cardiac surgery	3 (3.5)

Results presented as mean ± standard deviation/ number (%)
Abbreviations: NYHA: New York Heart Association; CVI: cerebrovascular insult; AVA: aortic valve area; AR: aortic regurgitation; LVEF: left ventricular ejection fraction; BAV: balloon aortic valvuloplasty; PCI: percutaneous coronary intervention

Indications for BAV included symptoms relief (47; 61.0 %), bridge to SAVR (1; 1.3 %) or TAVR (25; 32.5 %), hemodynamic unstable patients in cardiogenic shock or sepsis (1; 1.3 %), oncologic patients prior urgent non-cardiac surgery (3; 3.9 %) (Figure 1).

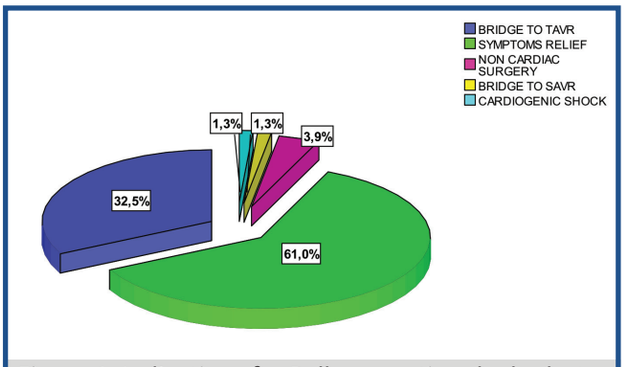


Figure 1. Indications for Balloon aortic valvuloplasty.
Abbreviations: BAV: Balloon aortic valvuloplasty; TAVR: Transcatheter aortic valve implantation; SAVR: surgical aortic valve implantation.

Hemodynamic results

After BAV we observed a significant decrease in mean trans-valvular gradient (from 43.8 ± 14.4 to 33.5 ± 12.3 mm Hg; $p < 0.01$) and an significant increase in aortic valve area (from 0.6 ± 0.2 to 0.8 ± 0.3 cm^2; $p < 0.01$). Procedural success was achieved in 73% of patients (reduction of peak to peak gradient on half), however 84% of patients improved clinically with reduction of pulmonary and right side congestion. Systolic pulmonary artery pressure, left ventricular ejection fraction and mitral regurgitation did not significantly change after BAV.

Table 2. Intrahospital complications after BAV.

Variables	Overall population BAV (n=77)
Overall major complication, n (%)	5 (6.5%)
Death for any causes, n (%)	1 (1.3%)
Vascular complications, n (%) Major Minor	 4 (5.3%) 11 (14.3%)
Myocardial infarction, n (%)	1 (1.3%)
Acute renal injury, n (%)	3 (4.0%)
Iodinated contrast induced thyrotoxicosis, n (%)	1 (1.3%)

Abbreviations: BAV: balloon aortic valvuloplasty

Procedural complications

Complications related to BAV are summarized in Table 2. Major intra-hospital complications occurred in 5 patients (6.5 %). We did not observe any death related to the BAV procedure. One patient died few days after BAV because of cardiogenic shock developed before the procedure. Major vascular complication occurred in 4 patients (5.2 %) where we observed pseudo-aneurysm leading to unplanned surgical intervention. Other vascular complications were classified as minor in 11 pa-

Table 3. Baseline characteristics according to the treatment after BAV in comparison to patients who underwent TAVR without previous BAV.

Variables	BAV	TAVR	TAVR only	p
N	57 (66.3)	19 (22.0)	9 (10.5)	
Age, y	81.9 ±5.4	83.1 ± 4.0	82.2 ±4.9	0.65
Men, n (%)	21 (36.8)	3 (15.8)	4 (44.4)	0.18
Logisitic EuroSCORE, %	20.9+13.5	17.2+7.4	13.8+6.8	0.18
BAV and PCI, n (%) (single procedure)	9 (15.8)	5 (26.3)	0	0.21
NYHA, n	3.1	2.9	2.2	<0.01
NYHA III and IV, n (%)	39 (68.4)	12 (63.2)	2 (22.2)	0.03
Diabetes, n (%)	11 (19.3)	7 (36.8)	3 (33.3)	0.25
Hypertension, n (%)	36 (63.2)	18 (94.7)	7 (77.8)	0.03
Hyperlipidemia, n (%)	6 (10.5)	6 (31.6)	0	0.03
Coronary artery disease, n (%)	22 (38.6)	10 (52.6)	4 (44.4)	0.56
COPD, n (%)	16 (28.1)	5(26.3)	2 (22.2)	0.93
Chronic renal failure, n (%)	22 (38.6)	7 (36.8)	1 (11.1)	0.27
Stroke, n (%)	10 (17.5)	2 (10.5)	1 (11.1)	0.71
Atrial fibrillation, n (%)	28 (49.1)	10 (52.6)	4 (44.4)	0.91
PAOD, n (%)	9 (15.8)	0	0	0.08
CABG, n (%)	8 (14.0)	3 (15.8)	1 (11.1)	0.95
Previous PCI, n (%)	12 (21.1)	3 (15.8)	2 (22.2)	0.87
Previous myocardial infarction, n (%)	6 (10.5)	0	0	0.21
Cancer, n (%)	11 (19.3)	3 (15.8)	1 (11.1)	0.81
Porcelain aorta, n (%)	0	1 (5.3)	0	0.17
Mean gradient , mm Hg before procedure	46.5±14.3	35.7±10.5	42.6±8.8	0.11
Mean gradient , mmHg after procedure	35.5±13.8	40.0±14.2	11.5±2.1	0.03 *0.51
AVA before procedure, cm^2	0.6±0.2	0.6±0.2	0.7±0.2	0.11
AVA after procedure, cm^2	0.7±0.2	0.8±0.1	1.6±0.2	<0.01 * 0.70
LVEF, %	52.9±14.9	48.0±15.1	51.7±2.9	0.63
Pulmonary hypertension, mmHg	50.5±16.5	43.5±7.5	44.3±7.5	0.36
Creatinin baseline, µmol/l	118.8±76.1	103.9±33.5	63.0±25.7	0.06
NTproBNP baseline, ng/l	9784.1±10271.4	7255.6±11347.9	2477,6±2554.5	0.33

Results presented as mean ± standard deviation/ number (%).
* p value related to the comparison of the group that underwent BAV versus the group that underwent TAVR after BAV.
Abbreviations: TAVR: transcatheter aortic valve replacement; TAVR only: TAVR patients without prior BAV; PCI: percutaneous coronary intervention; NYHA: New York Heart Association; COPD: chronic obstructive pulmonary disease; PAOD: peripheral arterial occlusive disease; AVA: aortic valve area; LVEF: left ventricular ejection fraction.

tients (14.3 %) – need for blood transfusion and pseudoaneurysm (2 cases) with no need for vascular surgery. In one patient we observed iodinated contrast induced thyrotoxicosis which was successfully treated with thyreo-static drugs. The most common complication was related to vascular access site. Acute myocardial infarction occurred in one case (1.3 %) and acute renal injury in 3 cases (4 %). We did not observe severe aortic regurgitation, stroke, permanent pacemaker requirement, tamponade or anular rupture in our patients.

Follow up and mortality

Patients left hospital 13.4 ± 10.8 days after BAV. 92% of the patients were in follow up of 16.1 ± 15.0 months. Within this period 20 patients were finally bridged to definitive therapy [TAVR n = 19 (22.1 %) and SAVR n = 1 (1.2 %)] and 66 (76.7 %) unsuitable for definitive therapy remained on medical therapy alone. In four patients BAV was repeated once and in two patients BAV twice during the follow up period. In 14 cases with concomitant coronary artery disease we performed BAV and PCI in a single procedure with no increase in peri-procedural complication rate. In 3 oncologic patients with severe aortic stenosis that required a major abdominal and gynecology surgery BAV and in one case BAV and PCI was done prior surgery. With angioplasty and BAV we achieved a good coronary artery flow and an increase in aortic valve area without any peri-procedural complications. Successful non-cardiac surgery was consecutively done in all the 3 cases[15].

Baseline characteristics of patients according to final treatment after BAV are presented in Table 3 and compared with the characteristics of patients who underwent

TAVR without previous BAV procedure. Overall, patients who underwent TAVR without previous BAV were less symptomatic and presented in lower NYHA functional class. There were no differences in AVA, mean trans-aortic gradient, pulmonary artery arterial pressure and mitral regurgitation severity between groups (Table 3).

Long-term follow-up was evaluated using Kaplan-Meier analysis, and survival curves according to treatment after BAV are shown in Figure 2. Patient bridged to TAVR had better outcomes compared with those treated by single BAV ($p < 0.01$). There was no significant impact on survival in patients where BAV was performed more than once and in patients where TAVR was performed without previous BAV (Figure 2–4).

Discussion

BAV was originally proposed as an alternative to SAVR for severe symptomatic AS, but it was rapidly neglected secondary to high restenosis rates and no impact on survival. In the TAVR era BAV was reported to be inferior to TAVR and comparable to medical therapy in terms of survival (16). We can confirm that single BAV, without bridge to TAVR/SAVR is associated to bad outcome. However, BAV might be a reasonable approach to offer symptomatic relief and improvement of the quality of life in selected high risk, comorbid patients and patients with short life expectancy. Current guidelines support this statement (recommendation Class IIb) and suggest this per-cutaneous treatment also as a bridge to TAVR/SAVR in hemodynamic unstable patients or in patients who require urgent major non-cardiac surgery (2, 17).

BAV as a definition therapy

In our cohort of very high risk patients with aortic stenosis, BAV was associated with statistically significant hemodynamic results with significant decrease of mean aortic gradient in BAV, BAV-TAVR and TAVR group from: 46.5±14.3 mmHg, 35.7±10.5 mmHg, 42.6±8.8 mmHg to 35.5±13.8 mmHg, 40.0±14.2 mmHg and 11.5±2.1, respectively. The major indication for BAV remains symptomatic relief (61.0 %) and due to low major complication rate (6.5 %) it is a reasonable approach. Vascular access site complications remain the principal procedural limitation but with the development of the technique over the years and with the use of vascular closure devices we may reduce the complication rate. In contrast to our experience, Eltchaninoff et al., reported an increase of aortic valve area > 1 cm^2 after BAV in most of the patients, recently (18). From this perspective, BAV may become a valid therapeutic option for high risk patients refused for surgery and unsuitable for TAVR. In our case AVA improved from 0.6 ± 0.2 to 0.8 ± 0.3 cm^2; $p < 0.01$. One of the reasons for less effective BAV comparing to the results published by Eltchaninoff et al. might be our conservative strategy. Namely, BAV is rather palliative procedure, therefore we were using undersized balloons for non-aggressive BAV. The rate of important AR and annulus damage is therefore zero. Most frequently we used BAV balloon of dimensions 20 mm, 23 mm and 25 mm in 78%, 18% and 4%, respectively.

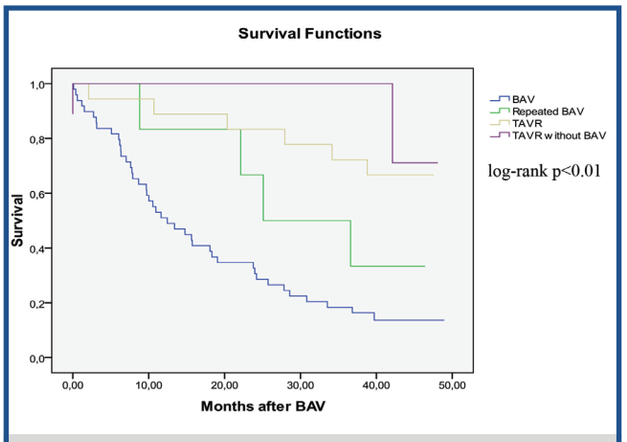


Figure 2. Kaplan-Meier estimated survival according to the percutaneous treatment of aortic stenosis.
Abbreviations: BAV: balloon aortic valvuloplasty; TAVR: transcatheter aortic valve replacement; TAVR only: TAVR patients without prior BAV

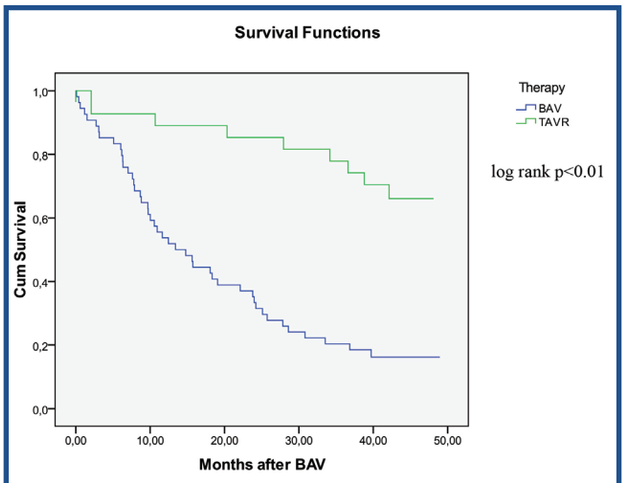


Figure 3. Kaplan-Meier estimated survival in BAV patients versus TAVR patients.
Abbreviations: BAV: balloon aortic valvuloplasty; TAVR: transcatheter aortic valve replacement.

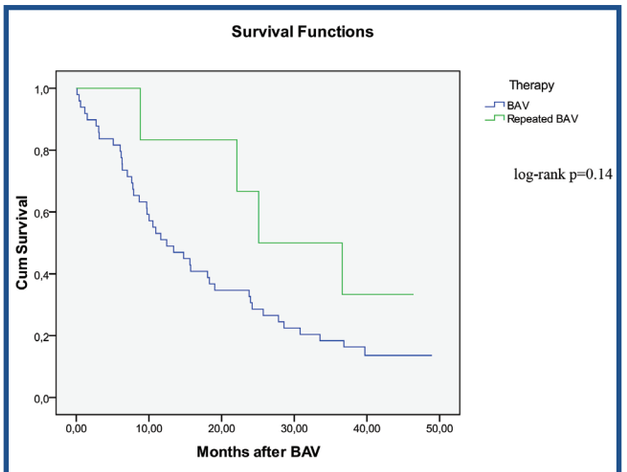


Figure 4. Kaplan-Meier estimated survival in patients who underwent a single BAV comparing to patients who underwent more than one BAV.
Abbreviations: BAV: balloon aortic valvuloplasty.

BAV as a bridge to TAVR/SARV

Soon after BAV we often observe an improvement of hemodynamic conditions; an increase of cardiac output, a reduction of pulmonary pressure and improvement of other heart failure clinical presentations (16). As a consequence BAV is recommended as a bridge to TAVR/SAVR in hemodynamic instable patients suffering from a potentially reversible acute state (for example sepsis or cardiogenic shock) (13). In our cohort we performed BAV in one patient (1.3 %) who presented in cardiogenic shock but despite the successful procedure he died because of the underlying disease. BAV may be also performed in patients who are good candidates for TAVR but per-cutaneous valve implantation is not available because of the economical and organisational issues. In potential TAVR candidates BAV can also serve as a diagnostic measure, which can help define the final therapeutic option: BAV or TAVR. In particular it can be used to asses the potential impact of left ventricular afterload reduction on improvement of low left ventricular ejection fraction, severe pulmonary hypertension and mitral regurgitation improvement.

BAV in cancer patients

We performed BAV in three oncologic patients that underwent major abdominal surgery soon after the percutaneous aortic procedure. Successful BAV and hemodynamic improvement should decrease the risk for abdominal surgery. In our experience the surgery was performed without cardiovascular complications. In selected high risk carcinoma patients BAV may be used as bridge to TAVI which can be done if there is no carcinoma relapse one year after non-cardiac surgery**.**

Long-term outcome after BAV

According to the results of PARTNER trial (16) we demonstrated that BAV remain a palliative measure, with no impact on long-term survival. The survival in patients bridged to TAVR after BAV was significantly higher than in those treated with BAV alone. In patients where BAV was performed more than once in comparison to single BAV we observe a trend of better outcome that is not statistically significant. We can speculate that early restenosis of the dilated aortic valve and consecutive relatively rapid re-increase in left ventricular afterload prevent ventricular reverse remodelling and exhibit the positive impact on the left ventricle we achieved early after BAV. With prevention of restenosis we may find a way to improve the outcome after BAV but until now no treatment strategy succeed in this attempt (20).

Conclusion

In conclusion, BAV is a feasible and reasonably safe approach to offer temporary relief in selected high risk patients with symptomatic severe aortic. BAV can be utilized as a part of a complex to improve the quality of life, decrease the surgical risk for major non-cardiac surgery or as a bridge to surgical or trans-catheter aortic valve implantation. BAV can also be used to select the best further treatment strategy (TAVR/SAVR or medical therapy) in patients with impaired LV function, pulmonary hypertension and important mitral regurgitation.

References

1. Rajamannan NM, Bonow RO, Rahimtoola SH. Calcific aortic stenosis: An update. Nat Clin Pract Cardiovasc Med 2007;4:254–262.
2. Vahanian A, Baumgartner H, Bax J, et al; Task Force on the Management of Valvular Hearth Disease of the European Society of Cardiology; ESC Committee for Practice Guidelines. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 2007;28:230–268.
3. Bonow RO, Carabello BA, Kanu C, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: Developed in collaboration with the Society of Cardiovascular Anesthesiologists: Endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons. Circulation 2006;114:e84–e231.
4. Iung B, Cachier A, Baron G, et al. Decision-making in elderly patients with severe aortic stenosis: Why are so many denied surgery? Eur Heart J 2005;26:2714–2720.
5. Cribier A, Sabin T, Saoudi N, et al. Percutaneous transluminal valvuloplasty of acquired aortic stenosis in elderly patients: An alternative to valve replacement? Lancet 1986;1:63–67.
6. McKay RG, Safian RD, Lock JE, et al. Balloon dilatation of calcific aortic stenosis in elderly patients: Post mortem, intraoperative, and percutaneous valvuloplasty studies. Circulation 1986;74:119–125.
7. Zimrin DA, Reyes PA, Miller KL, et al. Heart failure and "inoperable" aortic stenosis: Staged balloon aortic valvuloplasty and aortic valve bypass. Congest Heart Fail 2008;14:211–213.
8. Kitamura H, Doi T, Okabayashi H, et al. Percutaneous transluminal balloon aortic valvuloplasty with a small balloon as a bridge to surgery for severe aortic stenosis in an 83-year-old patient. Jpn J Thorac Cardiovasc Surg 2003;51:562–564.
9. Dauterman KW, Michaels AD, Ports TA. Is there any indication for aortic valvuloplasty in the elderly? Am J Geriatr Cardiol 2003;12:190–196.
10. Smedira NG, Ports TA, Merrick SH, Rankin JS. Balloon aortic valvuloplasty as a bridge to aortic valve replacement in critically ill patients. Ann Thorac Surg 1993;55:914–916.
11. Pena HP, Teixeira SL, Mandil A, et al. Aortic balloon valvuloplasty as a bridge to definitive therapy of severe aortic stenosis. Arq Bras Cardiol 1997;69:55–57.
12. Vahanian A, Alfieri O, Al-Atta N, et al. Transchateter valve implantation for patients with aortic stenosis: A position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI). EuroInterv 2008;4:193–199.
13. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;42(4):1–44.
14. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. Eur Heart J 2011;32(2):205–17.
15. Kogoj P, Devjak R, Bunc M. Balloon aortic valvuloplasty (BAV) as a bridge to aortic valve replacement in cancer patients who require urgent non-cardiac surgery. Radiol Oncol 2014;48(1):62–6.
16. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363(17):1597–607.
17. Nkomo VT, Gardin JM, Skelton TN, et al. Burden of valvular heart diseases: A population-based study. Lancet 2006;368:1005–1011.
18. Eltchaninoff H, Durand E, Borz B, et al. Balloon aortic valvuloplasty in the era of transcatheter aortic valve replacement: acute and long-term outcomes. Am Heart J 2014;167(2):235–40.
19. Kogoj P, Music S, Lakic N, et al. Balloon Aortic Valvuloplasty In Severe Aortic Stenosis And Prevention Of Restenosis In Elderly. J Am Coll Cardiol 2012;60:17.

Srce i krvni sudovi 2014; 33(1): 27-29

Prikaz slučaja

Successful transfemoral core valve aortic valve implantation in a patient with degenerated solofreedom biologic supravalvular aortic valve

Matjaž Bunc[1,4], Polonca Kogoj[1], Jana Ambrožič[1], Špela Mušič[2], Nikola Lakič[2], Borut Geršak[2]

[1]*Department of Cardiology, University Medical Centre Ljubljana, Zaloška c. 007, 1000 Ljubljana,* [2]*Department for Cardio and Vascular Surgery, University Medical Centre Ljubljana,* [3]*Department of Radiology,* University Medical Centre *Ljubljana, Zaloška c. 007, 1000 Ljubljana,* [4] *Institute for Pathopysilogy, School of Medicine, Zaloška c.002, 1000 Ljubljana*

Abstract Percutaneous aortic valve implantation (TAVI) is well established treatment option for high risp patients with severe aortic stenosis. Transcatheter aortic valve implantation (TAVI) is an attractive treatment option for patients with failing bioprostheses (valve-in-valve concept), especially in elderly patients with high risk for reoperation. Although clinical experience is still limited for this off-label indication, the procedure has been shown to be feasible in stented as well as stentless bioprostheses. We report a case of of 71-years old woman were CoreValve 23 mm (Medtronic, Inc., Minneapolis, Minnesota, USA) was implanted inside a degenerated Sorin Freedom SOLO bioprosthesis using transfemoral approach. Freedom SOLO bioprosthesis stentless bioprosthesis is sutured in supra-annular position and presents a TAVI challenge due to its proximity to coronary ostia. Careful pre-procedural planning with TEE and CTA is crucial. We decided for transfemoral approach with 23 m CoreValve implantation. Balloon valvuloplasty before TAVI with contrast injection may predict the final result and is helpful for procedure success and risk reduction. The final TAVR result was good. This case proves the ViV concept for stentless Freedom SOLO bioprosthesis.

Key words TAVI, SOLO Freedom, stentless bioprosthesis, degeneration, valve in valve

Background

The most effective treatment for patients with severe symptomatic aortic stenosis is surgical replacement of the valve.[1] Aortic valve replacement with a bioprosthesis is preferred, especially in older populations, due to its satisfactory hemodynamic performance without warfarin related complications. Sorin Freedom SOLO bioprosthesis (Sorin Biomedica Cardio, Saluggia, Italy) is implantated in the supra-annular position. According to available data the SOLO valve is durable with good hemodynamic performance and low complication rates.[2-4] In our institution more than 500 implantations were performed in the last 8 years.[5] It should not be unexpected that a considerable number of patients may require reintervention due to a dysfunctional bioprosthesis with structural valve deterioration. Surgical treatment of degenerated aortic bioprostheses is associated with an increased risk of morbidity and mortality, especially in elderly patients with significant co-morbidities. Therefore, transcatheter aortic valve implantation (TAVI) performed as valve in valve (VIV) technique appears as an attractive alternative treatment option.[6-9] Pericardial stentless aortic bioprosthesis Freedom Solo represents a challenge for VIV implantation due to its supra-annular position potentially leading to coronary obstruction.

We report a case of ViV implantation by transfemoral approach with a 23-mm self-expandable prosthesis CoreValve (Medtronic, Inc., Minneapolis, Minnesota, USA) inside a degenerated Sorin Freedom SOLO bioprosthesis.

Case presentation (Core Valve in Freedom Solo valve)

71-years old woman underwent surgical aortic valve replacement with a 25-mm Freedom Solo bioprosthesis in 2007. During the same surgical procedure bypass graft with *left internal mammary artery* (LIMA) left to LAD and venous grafts to the first (OM1) and second (OM2) obtuse marginal coronary artery was also done. Five years after the surgery she presented to our institution with dispnea (New York Heart Association functional class II to III). Echocardiographic examination revealed degeneration of the aortic bioprosthesis (mean gradient across the aortic valve of 28 mmHg and aortic valve area of 0.83 cm^2). She refused any other further evaluation and tre-

Correspondence to Matjaž Bunc, MD PhD, Professor of internal medicine and pathophysiology, University Medical Center Ljubljana, Zaloška c. 007, 1000 Ljubljana, Slovenia.

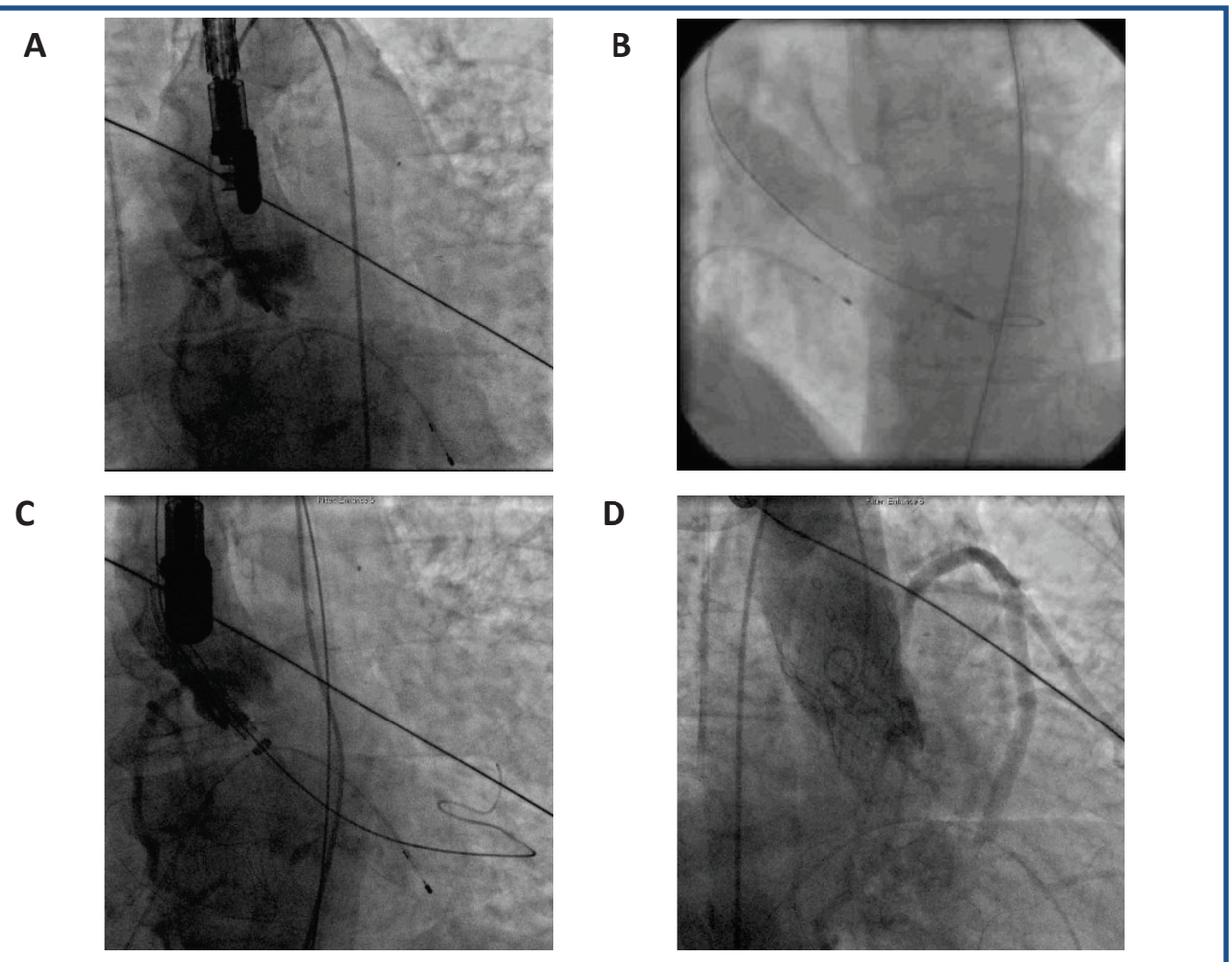


Figure 1: Valve in valve implantation

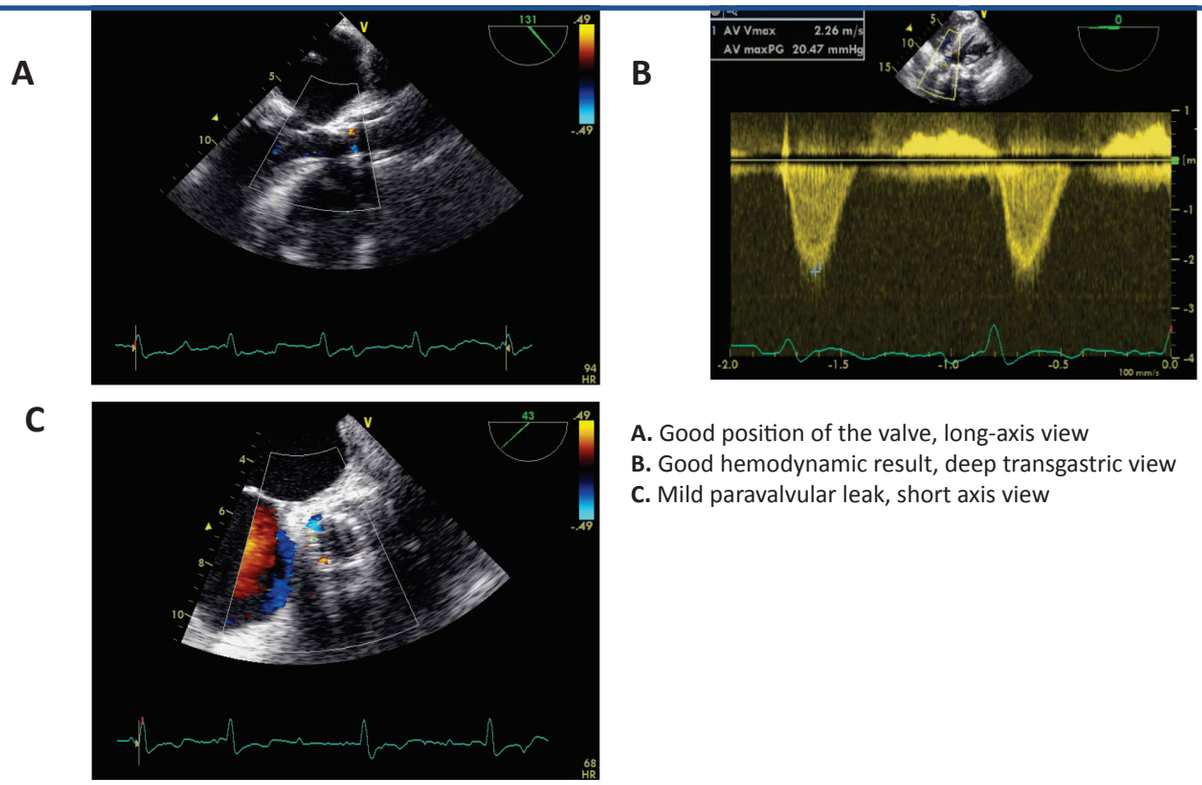
A. Orthogonal view before baloon valvuloplasty **B.** Baloon valvuloplasty
C. Valve positioning **D.** Final angiographic result

atment and was discharged. She presented again after one year with severe heart failure. An *echocardiogram* revealed a progression of the biologic aortic valve degeneration with severe aortic stenosis (mean gradient of 50 mmHg, aortic valve area of 0.6 cm^2) and mild to moderate aortic regurgitation. The global systolic function of the left ventricle was preserved with the ejection fraction of 65%. A severe pulmonary hypertension of 85 mmHg was also found. Cardiac catheterization showed patent coronary artery bypasses with no new significant disease on other coronary arteries. Due to several comorbidities (chronic obstructive pulmonary disease with severe obstructive and restrictive respiratory failure, chronic renal disease, diabetes on insulin, severe obesity, previous cardiac surgery) the surgical risk was high (logistic Euroscore of 31%) and she was refused for aortic valve re-replacement. TAVI was considered and shown to be feasible after morphological evaluation with multidetector computed tomography and transesophageal echocardiography.

One week after the admission we performed the percutaneus procedure under general anestesia. First we inserted a SPIDER Embolic Protection Device in the right internal carotid artery to prevent embolic events. Then balloon aortic valvuloplasty with aortic angiography was done for the final valvular sizing and to explore the anatomical relation of the opened surgical prosthesis leaflets to the coronary ostia (Figure 1 B). After the vuloplasty a 23-mm self-expandable CoreValve (Medtronic, Inc., Minneapolis, Minnesota, USA) was implanted via femoral access (Figure 1 C). The transcatheter prosthesis was expanded during rapid pacing under fluoroscopic and transesophageal guidance. The final angiographic result was excellent, showing good opening of the trancatheter valve leaflets and fully patent coronary ostia (Figure 3 D). Echocardiogram after implantation showed good hemodynamic properties of the transcatheter valve with a maximal gradient of 20 mmHg, estimated aortic valve area of 1.7 cm^2 and mild paravalvular regurgitation (Figure 2).

Discussion

Increased life expectancy and improvement in clinical outcome following surgery has led to an increasing number of elderly patients with a history of prior aortic valve replacement (AVR). As a consequence, a considerable number of patients may require reintervention due to a dysfunctional bioprosthesis with structural valve deterioration. Transcatheter aortic valve implantation (TAVI) has become an established surgical alternative in patients



A. Good position of the valve, long-axis view
B. Good hemodynamic result, deep transgastric view
C. Mild paravalvular leak, short axis view

Figure 2. Transesophageal echocardiographic assessment after valve-in-valve implantation of the self-expandable CoreValve

with aortic stenosis and severe comorbidities. Freedom Solo aortic valve is stentless bioprosthesis that is implanted in a supravalvular position, which is particularly beneficial in elderly patients with severely calcified aortic valves rendering difficult the conventional implantation in the annular position.[2,3,5]

During valve-in-valve implantation supra-annular bioprosthetic position presents a technical challenge since bioprosthetic leaflets may extent to aortic wall and potentially obstruct coronary ostia. Careful pre-procedural planning with multidetector computed tomography and three-dimensional transesophageal echocardiography is important for the assessment of aortic root anatomy, relationship of the bioprosthetic leaflet height in relation to coronary ostia and size of the prosthesis orifice.[10,11] In addition, balloon valvuloplasty before TAVI is useful for checking the position of the opened bioprosthetic leaflets in relation to coronary ostia and for final valvular sizing.

In the reported case we have shown that valve-in-valve procedure for failing supra-annular bioprosthesis Freedom Solo is feasibile, considering technical difficulties.

References

1. Vahanian A, Alfieri O, Andreotti F et al. Guidelines on the management of valvular heart disease (version 2012): The joint task force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2012;33:2451-96.
2. Aymard T, Eckstein F, Englberger L, Stalder M, Kadner A, Carrel T. The Sorin Freedom SOLO stentless aortic valve: technique of implantation and operative results in 109 pa-tients. J Thorac Cardiovasc Surg 2010;139(3):775-7.
3. Altintas G, Ilkay Diken A, Hanedan O, Yurdakok O, Ozyalcin S, Kucuker SA, Ozatik AMThe Sorin Freedom SOLO Stentless Tissue Valve. *ex Heart Inst J 2013;40(1):50-5.*
4. Beholz S, Claus B, Dushe S, Konertz W. Operative technique and early hemodynamic results with the Freedom Solo valve. J Heart Valve Dis 2006;15(3):429-32.
5. Gersak B, Gartner U, Antonic M. Thrombocytopenia following implantation of the stentless biological Sorin Freedom SOLO valve. J Heart Valve Dis 2011;20(4):401-6.
6. Dvir D, Barbanti M, Tan J, Webb JG. Transcatheter aortic valve-in-valve implantation for patients with degenerative surgical bioprosthetic valves. Curr Probl Cardiol. 2014 Jan;39(1):7-27.
7. Dvir D, Webb J, Brecker S, Bleiziffer S, Hildick-Smith D, Colombo A, Descoutures F, Hengstenberg C, Moat NE, Bekeredjian R, Napodano M, Testa L, Lefevre T, Guetta V, Nissen H, Hernández JM, Roy D, Teles RC, Segev A, Dumonteil N, Fiorina C, Gotzmann M, Tchetche D, Abdel-Wahab M, De Marco F, Baumbach A, Laborde JC, Kornowski R. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. Circulation. 2012 Nov 6;126(19):2335-44.
8. Azadani AN, Tseng EE. Transcatheter heart valves for failing bioprostheses: state-of-the-art review of valve-in-valve implantation. Circ Cardiovasc Interv 2011;1;4(6):621-8.
9. Bapat V, Attia R, Redwood S, Hancock J, Wilson K, Young C, Thomas M. Use of transcatheter heart valves for a valve-in-valve implantation in patients with degenerated aortic bioprosthesis: technical considerations and results. J Thorac Cardiovasc Surg. 2012 Dec;144(6):1372-9; discussion 1379-80.
10. Bapat VN, Attia R, Thomas M. Effect of Valve Design on the Stent Internal Diameter of a Bioprosthetic Valve: A Concept of True Internal Diameter and Its Implications for the Valve-in-Valve Procedure. JACC Cardiovasc Interv. 2014 Jan 9. pii: S1936-8798(13)01677-4.
11. Bapat VN, Attia RQ, Condemi F, Visagan R, Guthrie M, Sunni S, Thomas M. Fluoroscopic guide to an ideal implant position for Sapien XT and CoreValve during a valve-in-valve procedure. JACC Cardiovasc Interv. 2013 Nov;6(11):1186-94.

Srce i krvni sudovi 2014; 33(1): 30-34

Prikaz slučaja

Prve transkateterske implantacije aortne valvule u Srbiji 2014. godine

Milan Nedeljković, Vladan Vukčević, Branko Beleslin, Goran Stanković, Miodrag Tešić, Siniša Stojković, Dejan Orlić, [1]Ilija Bilbija, [1]Miloš Matković, [2]Tijana Simić, [3]Nemanja Menković, [4]Igor Mrdović, [5]Gian Paolo Ussia

Klinika za kardiologiju, Klinički centar Srbije, [1] Klinika za kardiohirurgiju, Klinički centar Srbije, [2] Centar za anesteziologiju i reanimatologiju, Klinički centar Srbije, [3] Klinika za radiologiju, Klinički centar Srbije, [4] Klinika za kardiologiju, Urgentni centar, Klinički centar Srbije, [5] Department of Cardiovascular Disease, Tor Vergata University of Rome, Rome, Italy

Sažetak U ovom prikazu opisujemo prva dva slučaja uspešne implantacije samooslobađajuće aortne valvule (CoreValve, Medtronic) transkateterskim putem koja je izvedena u Sali za kateterizaciju na Klinici za kardiologiju Kliničkog centra Srbije. Intervencije su izvedene kod pacijenata koji su imali tešku aortnu stenozu i visok rizik za hirurišku proceduru. Intervencije su uspešno izvedene i bez neposrednih i značajnih komplikacija. Posle uspešne implantacije ove dve aortne vavule transkateterskim putem naša interventna kardiologija nastavlja sa novim entuzijazmom realizaciju strateškog razvoja programa lečenja strukturnih bolesti srca u Sali za kateterizaciju.

Ključne reči: teška aortna stenoza, transkateterska zamena aortne valvule (TAVR)

Uvod

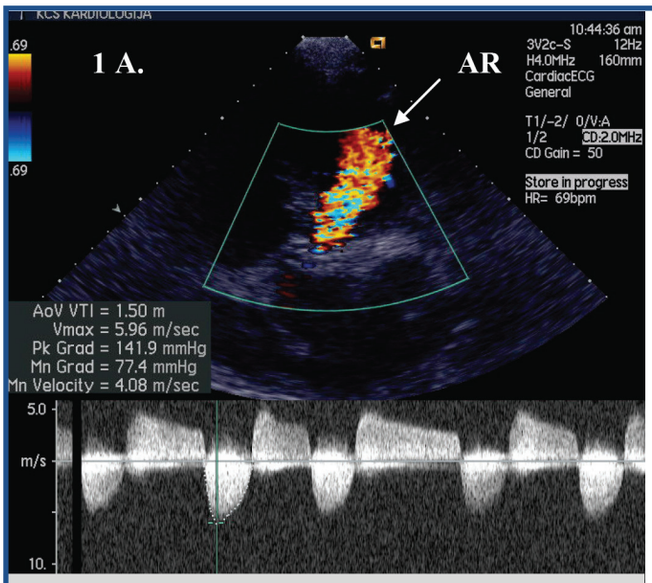
Pacijenti sa teškom aortnom stenozom predstavljaju specifičnu grupu pacijenata, ne samo zbog često delikatne i ne uvek jednostavne dijagnostike već i zato što predstavljaju poseban terapijski izazov s obzirom na često odmaklu životnu dob i prateće komorbiditete. Kao alternativa hirurškom lečenju poslednjih nekoliko godina naročito se razvila mogućnost zamene aortne valvule ne-hirurškim, odnosno perkutanim i transkateterskim putem.[1, 2] Rezultati su pokazali da se transkateterska zamena aortne valvule (TAVR) pokazala kao uspešna terapijska opcija kod pacijenata koji imaju visok operativni rizik[3, 4, 5] i kao takva je prihvaćena alternativa od strane Evropskog kardiološkog društva.[6] S obzirom na bogatu tradiciju srpske interventne kardiologije koja se uvek trudila da bude aktuelna i primeni sva najnovija dostignuća u invazivnoj dijagnostici i terapiji kardioloških pacijenata, u toku prošlog meseca smo uspeli da realizujemo višegodišnju ideju o uvođenju ovog načina lečenja u naš centar. U ovom prikazu pokazujemo iskustva sa naša prva dva pacijenta koja su urađena u prisustvu proktora prof. Gian Paola Ussie iz Rima u Sali za kateterizaciju Klinike za kardiologiju Kliničkog centra Srbije, od strane interventnih kardiologa, a uz podršku kardiohirurga, anesteziologa i kliničkih kardiologa.

Prikaz slučaja 1.

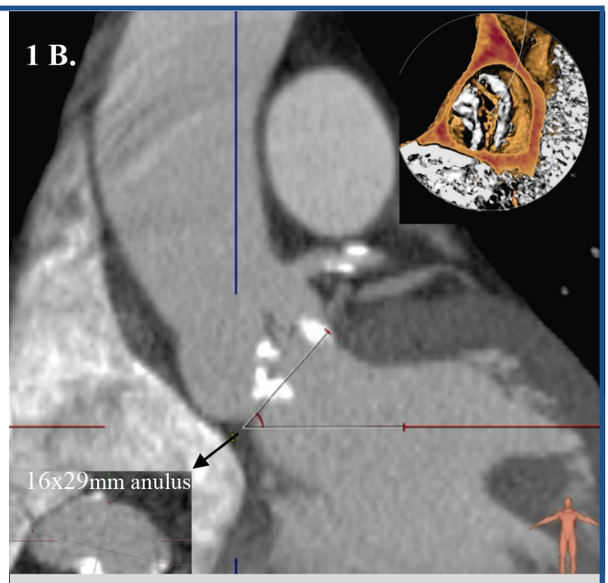
Bolesnik star 77 godina sa kompletnom aortnom manom je primljen radi izvođenja TAVR procedure. Kao glavne tegobe navodi brzo zamaranje (NYHA III) i gušenje praćeno anginoznim tegobama. Od faktora rizika za koronarnu bolest bolesnik navodi hipertenziju, hiperlipoproteinemiju i dijabetes tip 2. Pacijent od ranije ima permanentnu fibrilacije pretkomora. U sklopu pripreme za TAVR proceduru prethodno je urađena koronarografija, gde je nađena i angiografski značajna stenoza na ostiumu RCA koja je lečena metalnim stentom (Liberte Monorail, 3.5x32 mm). Tako da je pacijentu pored antikoagulante terapije uvedena i dvojna antiagregaciona terapija. Pacijent je odbio predloženu hirurišku zamenu aortne valvule.

Ehokardiografskim pregledom je utvrđeno postojanje izrazito kalcifikovane bivelarne aortne valvule sa tesnom aortnom stenozom i 3+ aortnom regurgitacijom. Dopperom je registrovan maksimalni gradijentom preko valvule od 142 mmHg, srednji 77 mmHg, a izračunata površina ušća je bila 0.58 cm² (Figura 1a). U uvećanoj levoj pretkomori (53 mm) registrovna je mitralna regurgitacija 2+. Leva komora je bila normalnih dimenzija (54/31 mm), koncentrično hipertrofičnih zidova (11 mm), očuvane ukupne sistolne funkcije (EF 65 %). De-

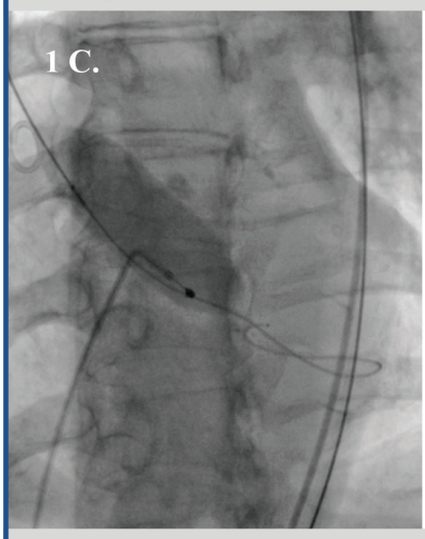
Adresa za korespodenciju: Branko Beleslin, Klinika za kardiologiju, Klinički centar Srbije, Višegradska 26, Beograd, Srbija, E-mail: branko.beleslin@gmail.com



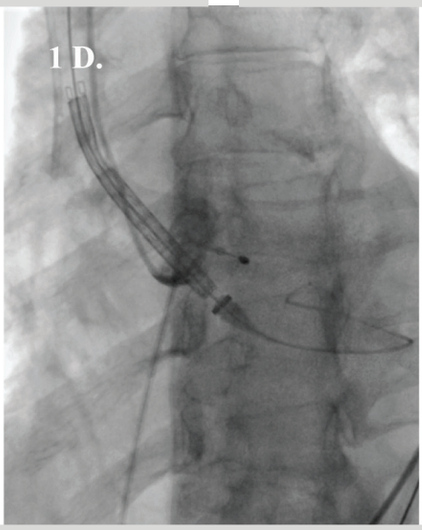
1a. Gradijent nad aortnom valvulom pre intervencije



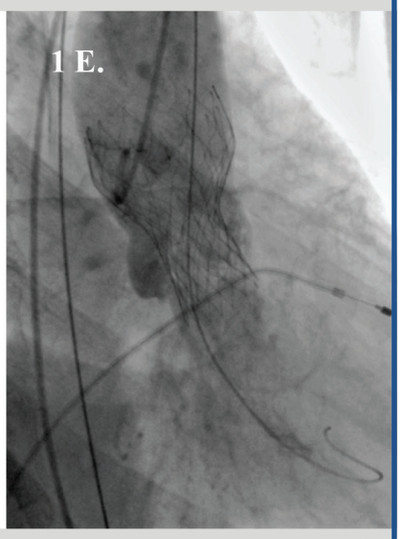
1b. Veličina aortnog anulusa i izgled aortne valvule na MSCT-u



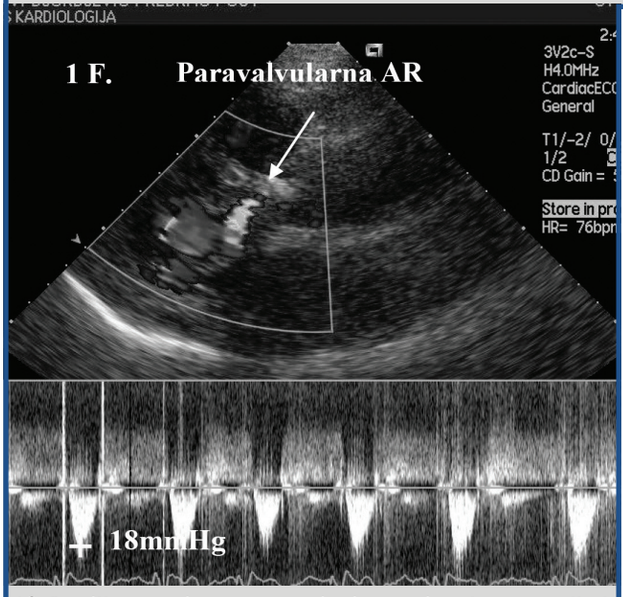
1c. Valvuloplastika aortne valvule



1d. Pozicioniranje aortne valvule



1e. Paravalvularna aortna regurgitacija na aortografiji



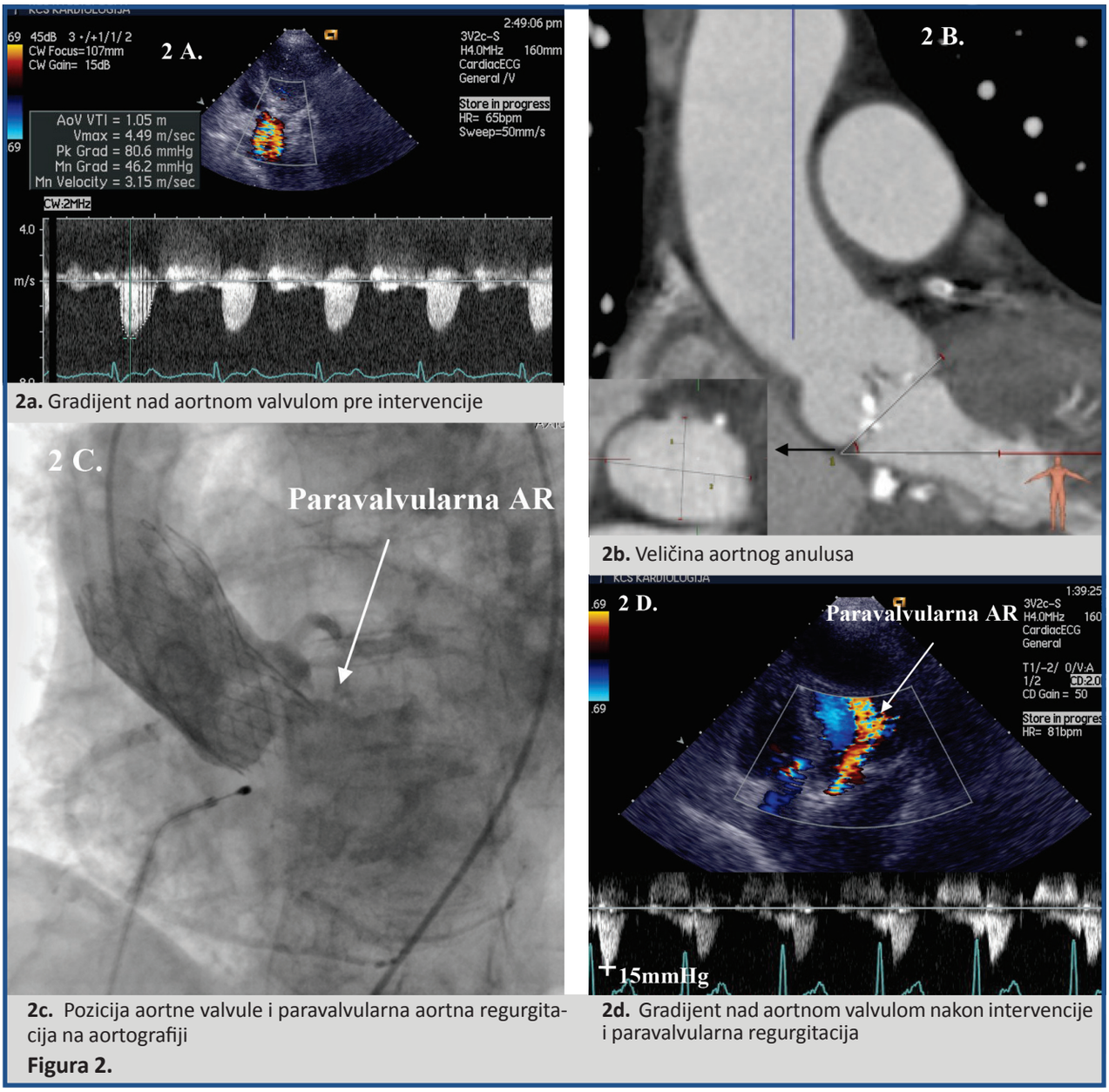
1f. Gradijent nad aortnom valvulom nakon intervencije i paravalvularna regurgitacija

Figura 1.

sne srčane šupljine su bile normalnih dimenzija. Registrovana je trikuspidalna regurgitacija 2+, a indirektno procenjen pritisak u desnoj komori je bio 62 mmHg.

Na multislajsnoj kompjuterizovanoj tomografiji (MSCT) je izmerena veličina aortnog anulusa 16x29 mm (Figura 1b), kao i ostale dimenzije aorte: bulbus aorte 30 mm, sinotubularni spoj aorte 31 mm, ascedentna aorta 39 mm. Takođe, potvrđeno je postojanje izražene kalcifikovane bivelarne aortne valvule (Figura 1b), što je tehnički predstavljalo teži slučaj za pozicioniranje i implantaciju valvule.

Pacijent je prvo uveden u totalnu intravensku analgo-sedaciju (prisutan kateter u desnoj jugularnoj veni, arterijska kanila u radijalnoj arteriji uz stalni monitoring centralnog venskog i arterijskog pritiska, EKG-a i saturacije), a potom je hiruški preparisana zajednička desna femoralna arterija u koju je plasiran uvodnik od 18 F, dok su u levom ingvinalnom predelu plasirana 2 uvodnika 6 F: jedan u levu zajedničku femoralnu arteriju preko koga je postavljen pig-tail kateter u ushodnu aortu i drugi u levu femoralnu venu radi plasiranja pejsing katetera u desnu komoru. Uz pomoć levog Amplatz katetera 2



2a. Gradijent nad aortnom valvulom pre intervencije

2b. Veličina aortnog anulusa

2c. Pozicija aortne valvule i paravalvularna aortna regurgitacija na aortografiji

2d. Gradijent nad aortnom valvulom nakon intervencije i paravalvularna regurgitacija

Figura 2.

prošlo se suženo aortno ušće i zamenjena je meka žica za tvrdu Amplatz Super Stiff žicu vodič u levu komoru. Nakon zamene meke za tvrdu žicu, urađena je predilatacija aortne valvule balonom Nucleus 22x40 mm (Nu-Med Canada Inc.) (Figura 1c) tokom brzog pejsinga (Fr-180/min.) sa elektrodom postavljenom u vrh desne komore. Nakon toga je uz pomoć aortografije i pig-tail katetera, koji se pozicionira u nekoronarni sinus, i služi i kao marker za pozicioniranje valvule i za opacifikaciju korena aorte, pozicionirana (Figura 2d) i implantirana samoekspandirajuća valvula CoreValve (Medronic) veličine 29 mm. Na kontrolnoj aortografiji je viđena paravalvularna aortna regurgitacija 1+ sa uredno pozicioniranom valvulom na aortnoj poziciji (Figura 1e) i gradijentom do 20 mmHg. Procedura je završena hirurškom suturom zajedničke desne femoralne arterije.

Kontrolni eho srca nakon dva dana od intervencije je ukazao na dobru poziciju valvule, sa maksimalnim gradijentom nad aortom od 18 mmHg i sa postojanjem 1+ paravalvularne AR (Figura 1f). Mitralna regurgitacija nakon intervencije je bila 1+, dok je indirektno izmeren pritisak u desnoj komori bio 45 mmHg. Nisu registrovani znaci perikardnog izliva, kao ni segmentni ispadi kinetike leve komore. Tokom hospitalizacije došlo je do razvoja anemije kao posledice gastroenterološkog krvarenja – gastroskopski nađene erozije antruma želuca i bulbusa dvanaestopalačnog creva sa jednom linearnom ulceracijom prekrivenom fibrino – što je bilo praćeno značajnim padom hemoglobina sa 110 gr/L na 81gr/L, pa je bolesnik primio 4 doze koncentrovanih eritrocita, kao i inhibitore protonske pumpe. Po kliničkom i laboratorijskom poboljšanju opšteg stanja, pacijent je otpušten iz bolnice na antikoagulantnoj terapiji i duploj dozi klopidogrela zbog utvrđene rezistencije na multiplate agregometriji.

Prikaz slučaja 2.

Bolesnica stara 79 godina je, zbog visokog rizika za hiruško lečenje tesne aortne stenoze, primljena radi perkutane implantacije aortne valvule (TAVR).

Kao glavne tegobe navodi brzo zamaranje (NYHA II-III) i gušenje. Aprila 2012. godine zbog tipičnih anginoznih bolova urađena je koronarografija, a potom i zbog značajnih stenoza urađena perkutana koronarna intervencija (PCI) sa implantacijom jednog stenta sa oslobađanjem leka (DES) u proksimalni segment LAD (Promus, 2.75x16 mm), jednog DES stenta u distalnom segmentu RCA (Promus, 3x20 mm), a na PL grani RCA ugrađen je metalni stent (Integrity, 2,5x22 mm). Na kontrolnoj koronarografiji koja je urađena pred TAVR intervenciju na mestu prethodno implantiranih stentova nije bilo angiografski značajnih stenoza. Od faktora rizika za koronarnu bolest bolesnica navodi hipertenziju i hiperlipoproteinemiju.

Ehokardiografskim pregledom je utvrđeno postojanje tesne aortne stenoze sa trivelarnom valvulom, fibrozno izmenjenih, umereno kalcifikovanih listića. Dopplerom je registrovan maksimalni gradijentom preko valvule od 81 mmHg, srednji 46 mmHg, a izračunata površina ušća je bila 0.7 cm² (Figura 2a). Takođe je utvrđeno postojanje kalcifikovanog posteriornog dela mitralnog anulusa uz rigidne pokrete zadnjeg mitralnog listića sa smanjenom površinom mitralnog ušća (1,75 cm²). U uvećanoj levoj pretkomori (50 mm) registrovna je mitralna regurgitacija 2–3+. Leva komora je bila normalnih dimenzija (46/24 mm), koncentrično hipertrofičnih zidova (12 mm), očuvane ukupne sistolne funkcije (EF 65 %). Desne srčane šupljine su bile normalnih dimenzija. Registrovana je trikuspidalna regurgitacija 2+, a indirektno procenjen pritisak u desnoj komori je bio 86 mmHg.

Na multislajsnoj kompjuterizovanoj tomografiji (MSCT) je izmerena veličina aortnog anulusa 17x25 mm (Figura 2b), kao i ostale relevantne dimenzije aorte za TAVR intervenciju: bulbus aorte 31mm, sinotubularni spoj aorte 29 mm, ascedentna aorta 32 mm.

Pacijentkinja je prvo uvedena u totalnu intravensku analgo-sedaciju (prisutan kateter u desnoj jugularnoij veni, arterijska kanila u radijalnoj arteriji uz stalni monitoring centralnog venskog i arterijskog pritiska, EKG-a i saturacije), a potom hiruški preparisana zajednička desna femoralna arterija u koju je plasiran uvodnik od 18 F, dok su u levom ingvinalnom predelu plasirana 2 uvodnika 6 F: jedan u levu zajedničku femoralnu arteriju preko koga je postavljen pig-tail kateter u ushodnu aortu i drugi u levu femoralnu venu radi plasiranja pejsing katetera u desnu komoru. Po plasiranju pig-tail katetera u levu komora postavljena je tvrda Amplatz Super Stiff žica vodiča u levu komoru i preko nje je urađena predilatacija aortne valvule balonom Nucleus 20x40 mm (NuMed Canada Inc.) pod uslovima brzog pejsinga (Fr-180/min,). Nakon toga je uz pomoć aortografije sa pig-tail katetera, koji je postavljen u nekoronarni sinus, pozicionirana i implantirana samoekspandirajuća valvula CoreValve (Medronic) veličine 26 mm. Na kontrolnoj aortografiji je viđena 1–2+ paravalvularna regurgitacija sa uredno pozicioniranom valvulom na aortnoj poziciji (Figura 2 c) i gradijentom do 15 mmHg. Procedura je završena hirurškom suturom zajedničke desne femoralne arterije.

Kontrolni eho srca nakon dva dana od intervencije je ukazao na dobru poziciju valvule, sa maksimalnim gradijentom nad aortom od 15 mmHg i sa postojanjem 1–2+ paravalvularne regurgitacije (Figura 2d). Takođe, registrovano je smanjenje mitralne regurgitacije na 1–2+, kao i značajan pad indirektno izmerenog pritiska u desnoj komori (33 mmHg). Nisu registrovani znaci perikardnog izliva, kao ni segmentni ispadi kinetike leve komore. Nije bilo komplikacija u postoperativnom toku i pacijentkinja je u dobrom stanju otpuštena posle 7 dana iz bolnice uz dvojnu antitrombocitnu terapiju.

Diskusija

Aortna stenoza je postala najčešća valvularna mana u razvijenom svetu sa učestalošću od 2–7 % kod pacijenata preko 65 godina[6]. Najčešće se susrećemo sa degenerativnom kalcifikovanom aortnom stenozom, druga najčešća etilogija je kongenitalna kod mlađe populacije, ali i starijih kao što je slučaj sa postojanjem bivelarne aortne valvule kod našeg prvog pacijenta, dok je reumatska etiologija vrlo retka. Bolest ima hroničan i progresivan tok i dugo je asimptomatska, međutim kada pacijenti pređu u simptomatsku fazu (dobro poznati trijas: bolovi u grudima, gubitak svesti, zamor pri naporu), bolest ima ubrzan i „maligan" tok sa preživljavanjem od 15–50 % za 5 godina[6]. Ehokardiografija je dominantna dijagnostička metoda posle utvrđivanja šuma na poziciji aortne valvule, sa Doppler merenjem gradijenta preko aortne valvule za procenu značajnosti stenoze. Značajnom aortnom stenozom se smatra ona koja ima površinu manje od 1cm², posebno <0.8 cm², ili u odnosu na masu tela <0.6 cm²[6]. Granična vrednost za značajnu aortnu stenozu je srednji gradijent pritiska između leve komore i aorte od 40 mmHg pod uslovima normalnog protoka. U slučaju male površine ušća i niskog gradijenta treba napraviti dodatnu evaluaciju funkcije leve komore i testiranje, često sa dobutamin stres ehokardiografskim testom radi procene težine aortne stenoze. U pripremi pacijenata za izvođenje TAVR neophodna je jasna procena težine aortne stenoze, simptomatologije, ehokardiografski nalaz i kardiohirurška procena operativnog rizika i njihova saglanost za izvođenje procedure. Operativni mortalitet za osobe preko 70 godina je 4–8 % i povećava se sa godinama, komorbiditetima, plućnom hipertenzijom, prethodnim operacijama i lošom funkcijom leve komore[6].

Drugi dijagnostički stub za pripremu ovih pacijenata predstavlja izvođenje MSCT snimanja sa evalucijom dimenzija korena aorte i pristupnih mesta femoralne i supklavijalne arterije koje moraju biti dovoljno široke i bez tortuoziteta zbog postavljanja dugačkog uvodnika veličine 18 F (oko 6 mm, što je i najmanja neophodni dijametar arterija).

TAVR se za sada preporučuje kod pacijenata koji su visokorizični za hirurišku proceduru, što se procenjuje skorom EuroSCORE ≥20 % ili STS ≥10 %. Ali s obzirom da nijedan skor nije idealan, najvažnija je procena opšteg stanja pacijenta, težine komorbiditeta i drugih stanja (npr. prethodna CABG ili porcelan aorta) koji daju prednost perkutanoj proceduri[6]. U dijagnostičkoj pripremi pacijenta neophodan je i prethodni pregled anesteziologa s obzirom da se procedura radi u intravenskoj analgo-sedaciji, ali ima i centara koji ovu procduru već izvode samo u lokalnoj anesteziji.

Što se tiče dostupnih aortnih valvula, najveći deo procedura se izvodi sa samooslobađajućom valvulom CoreValve (Medtronic, USA) ili balon-oslobađajućom aortnom valvulom Sapien (Edwards, USA) i njihova primena je potvrđena odličnim rezultatima u PARTNER studiji i ADVANCE registru[7,8]. Kod naših pacijenata smo uspešno ugradili CoreValve aortne valvule bez neposrednih komplikacija. Što se tiče komplikacija posle implantacije, one se shematski mogu podeliti u 4 kategorije: AV blok, moždani udar, vaskularne komplikacije na mestu punkcije i pojava paravalvularne aortne insuficijencije. Zbog mogućnosti razvoja ovih komplikacija i adekvatnog monitoringa neophodno je ove pacijente posle intervencije dalje pratiti u intenzivnoj (obično prva dva dana) i potom poluintenzivnoj nezi sledećih nekoliko dana. Kod našeg prvog pacijenta, zbog prisustva trojne antitrombocitne terapije, došlo je do razvoja krvarenja iz gastrointestanalnog trakta koje je uspešno lečeno i tretirano konzervativnim merama.

Specifičnosti naša prva dva pacijenta su bile takve da se kod prvog radilo o bikuspidnoj aortnoj valvuli koja nije idelna opcija za TAVR zbog obično značajne mase kalcifikacija na zaliscima i više geometrijski izmenjene valvule koja može otežati pozicioniranje i dovesti do značajne paravalvularne aortne regurgitacije posle intervencije, kao i prisustvo trojne antitrombocitne terapije. Što se tiče druge pacijentkinje, ona je imala pridruženu mitralnu manu i značajnu plućnu hipertenziju. Međutim, sama za sebe mitralna mana nije bila indikovana za operaciju, a posle implantacije došlo je do značajnog smanjenja plućne hipertenzije. Druga činjenica je da su oba pacijenta imala i prethodne značajne koronarne stenoze koje su lečene PCI procedurom i koje ako postoje, treba tretirati najmanje mesec dana pre TAVR, ili ako su rađene ranije, treba proveriti stanje na koronarnim arterijama, što je i urađeno kod oba naša pacijenta. Inače ovi pacijenti ne zahtevaju primenu oralne antikoagulantne terapije, osim parenetralne antikoagulantne u neposrednom postoperativnom toku, već samo uz 3–6 meseci dvojne antitrombocitne terapije, a potom samo jednog antitrombnog leka.

Sa ova prva dva pacijenta kojima je ugrađena transkateterskim putem aortna valvula verujemo da otvaramo u punoj meri program lečenja strukturnih bolesti srca u Sali za kateterizaciju koji se odnosi na zatvaranje ASD-a, primenu matičnih ćelija transkatetreskim putem, TAVR procedure, zatvaranja aurikule leve pretkomore kod pacijenata sa kontraindikacijom za oralnu antikoagulantnu terapiju, a verujemo u skorijoj budućnosti i lečenje mitralne insuficijencije, kao i druge nove tehnike koje pokažu pozitivne rezultate.

Zahvalnost: Želimo da se zahvalimo Fondu Srbije za zdravstveno osiguranje, posebno direktoru prof. Momčiću Babiću i g. Nikoli Pandrcu, kao i rukovodstvu Udruženja kardiologa Srbije na čelu sa prof. dr Zoranom Perišićem na razumevanju i finansijskoj podršci u uvođenju ove metode u našu zemlju. Takođe se zahvaljujemo firmi *Bimed* i *Medtronic* na brzoj i efikasnoj podršci u realizaciji ovog projekta.

Literatura

1. Zajarias A, Cribier AG. Outcomes and safety of percutaneous aortic valve replacement. J Am Coll Cardiol 2009;53:1829-1836.
2. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-1607.
3. Ussia GP, Barbanti M, Petronio AS, et al; CoreValve Italian Registry Investigators. Transcatheter aortic valve implantation: 3-year outcomes of self-expanding CoreValve prosthesis. Eur Heart J 2012;33:969-976.
4. Zahn R, Gerckens U, Linke A, et al; German Transcatheter Aortic Valve Interventions-Registry Investigators. Predictors of one-year mortality after transcatheter aortic valve implantation for severe symptomatic aortic stenosis. Am J Cardiol 2013;112:272-279.
5. Moat NE, Ludman P, de Belder MA, et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol 2011;58:2130-2138.
6. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2012;33:2451-2496.
7. Kodali SK, Williams MR, Smith CR, et al; on behalf of PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med 2012;366:1686-1695.
8. Genereoux P, Head SJ, Wood DA, et al. Transcatheter aortic valve implantation 10-zears anniversary: review of current evidence and clinical implications. Eur Heart J 2012; doi: 10.1093/eurheartj/ehs220.

Abstract

First transcatheter implantations of aortic valve in Serbia 2014.

Milan Nedeljković, Vladan Vukčević, Branko Beleslin, Goran Stanković, Miodrag Tešić, Siniša Stojković, Dejan Orlić, [1]Ilija Bilbija, [1]Miloš Matković, [2]Tijana Simić, [3]Nemanja Menković, [4]Igor Mrdović, [5]Gian Paolo Ussia

Clinic for cardiology, Clinical center of Serbia, [1] Clinic for cardiac surgery, Clinical center of Serbia, [2] Center for anesteziology and reanimation, Clinical center of Serbia, [3] Clinic for radiology, Clinical center of Serbia, [4]Clinic for cardiology, Emergency center, Clinical center of Serbia, [5]Department of Cardiovascular Disease, Tor Vergata University of Rome, Rome, Italy

We present first two cases of successful transcatheter implantation of self-expandable aortic valve (Corevalve, Medtronic) performed at Cardiology clinic, Clinical center of Serbia. The procedures were performed in patients with severe aortic stenosis and high surgical risk. Both interventions were successfully performed without significant periprocedural complications. With successful implementation of those 2 aortic valves, our center continues with new enthusiasm strategic development of program of percutaneous treatment of structural heart diseases.

Key words: *severe aortic stenosis, transcatheter aortic valve replacement (TAVR)*

Srce i krvni sudovi 2014; 33(1): 35-40

Pregledni rad

Left atrial appendage closure with the Watchman device - new option for patients with atrial fibrillation and high-risk of thromboembolic events

Anna Olasińska-Wiśniewska, Marek Grygier

Poznan University of Medical Sciences, Poland

Atrial fibrillation and left atrial appendage

The atrial fibrillation (AF) is the most common cardiac tachyarrhythmia. It affects approx. 1% of general population[1] and this percentage increases with age affecting about 3,8% of patients over 60 years and 9% of patients over 80 years[1]. Stroke is the most debilitating and life-threatening complications of AF. The arrhythmia is associated with even a 5-fold risk of stroke.[2,3] The frequency of AF in stroke patients admitted to medical departments ranges from 6,5% in younger patients (50-59 year)[2] to over 30% in octogenarians.[2,4,5] Thus elderly patients are not only prone to AF, but their stroke risk is also higher. Strokes related to AF are associated with worse prognosis, worse neurological outcome and higher rate of medical complications, including pneumonia, pulmonary oedema and heart failure compared with strokes of other than AF etiology.[4] The probability of remaining disabled or handicapped is increased by almost 50%.[5] The in-hospital and long-term mortality rate are also higher in patients with AF.[4,5]

Blackshear and Odell[6] reviewed twenty three studies that evaluated the presence and location of left atrial thrombus by transoesophageal echocardiography, autopsy or operation. The analysis revealed that left atrial thrombi occur in left atrial appendage in 91% of non-rheumatic atrial fibrillation and in 57% of rheumatic mitral valve disease. Non-rheumatic atrial fibrillation is probably responsible for 15–20% of cerebrovascular accidents of ischaemic origin.[7,8]

The left atrial appendage (LAA) is a remnant of the primary left atrium which forms during third week of embryonic development.[9] The proper left atrial cavity develops later and is formed from the outgrowth of the pulmonary veins.

The LAA has a tubular, hooked and trabeculated structure[9] with considerable heterogeneity among individuals in size, shape, wall thickness and morphology.[10] It is more distensible than the left atrium proper and may augment haemodynamic function as a decompression chamber by modulating left atrial pressure – volume relations in states of increased left atrial pressure and volume overload.[9,11] The LAA also contains stretch receptors that may regulate thirst [11] and other endocrine cells that produce atrial natriuretic peptide[7,9,11] and help regulating fluid balance. The cardiocytes of the LAA contain the greatest density of atrial natriuretic peptide granules found in the left atrium.[9,11] Several authors reported fluid retention after bilateral atrial appendectomy concomitant to maze procedure.[12-14] In those patients in whom the right atrial appendage was preserved the production of atrial natriuretic peptide was maintained resulting in better diuresis in the postoperative period.[12-14] The LAA may be also the site of triggers that can induce episodes of AF and of re-entrant drivers that may participate in the AF maintenance. In AF, remodeling as well as impaired blood flow occur in left atrial appendage.[11] These pathological conditions may lead to stasis and thrombus formation.[9] The degree of stasis in LAA is substantially worse than in the right atrial appendage because of differences in the anatomy and blood flow in both appendages.[7]

Strategies of pharmacological stroke prevention in atrial fibrillation

According to current guidelines[3] classic OAC and new OAC (NOAC) are recommended to prevent thromboembolic events in atrial fibrillation patients. The CHA_2DS_2VASc score was implemented for stroke risk assessment and to guide treatment choice. Stroke in the past and age over 75 years, based on the CHA_2DS_2VASc score, are two factors strong enough to start OAC therapy in patients with AF. The decision to begin therapy must stay in balance with risk of major bleeding, especially intracranial, which is the most serious complication of this therapy with a high risk of disability and death.[3] Therefore HAS-BLED score should be also calculated in each patient to evaluate the risk of bleeding.

There are however even more difficulties associated with OAC, including drug interactions, dietary restriction, poor patient adherence to treatment, labile interna-

Correspondence to Anna Olasińska-Wiśniewska MD, PhD, Department of Cardiology, Poznan University of Medical Sciences, Dluga ½, 61-848 Poznań, Poland, Phone: +48501066432, fax.: +48618549223, e-mail: mgrygier@wp.pl

tional normalized ratio (INR) and problematic decisions during urgent invasive procedures.[8] The majority of strokes in patients who started OAC occur in subjects who have discontinued OAC or whose INR is subtherapeutic.[15] Moreover, several studies[5, 16] proved that OAC therapy is not properly implemented. Euro Heart Survey Investigators[16] showed that, despite strong recommendations, OAC therapy was properly prescribed only in 60% of high risk patients, whereas 28% were undertreated and 11% overtreated. Similar results were presented in systematic review of 54 studies performed by Ogilvie et al.[17] with treatment level ranging from 39% to 92,3% of high risk patients based on the CHADS2 risk score. High discontinuation rate (30%) was also underlined[17]. Moreover, there are several contraindication for OAC, including evidence of active bleeding, history or predisposition to intracranial bleeding, uncontrolled severe hypertension, recent brain, eye or spinal cord surgery or injury, propensity for recurrent falling, inability for INR monitoring, and patient non-compliance.

The NOAC have shown non-inferiority compared with classical OAC and better safety limiting the number of intracranial hemorrhage[18,19]. Nevertheless, many problems with oral anticoagulation remained unresolved. Dabigatran and rivaroxaban are contraindicated in severe kidney disease (with creatinine clearance lower than 30 mL/min), and the dose should be reduced in the presence of high bleeding risk (HAS-BLED score ≥3), moderate kidney disease (with creatinine clearance 30-49 mL/min), as well as in elderly patients (≥80 years) and if concomitant use of interacting drug (werapamil) is necessary for dabigatran. The risk of major bleeding is similar among NOAC and estimated as 3,36-3,6% per year during rivaroxaban therapy[18,19], 3,4% per year during warfarin therapy[19] and 2,71% per year during treatment with dabigatran 110mg daily and 3,11% per day with the daily dose 150mg of dabigatran[18]. ROCKET-AF study[19] revealed that rates of intracranial hemorrhage were significantly lower in the rivaroxaban group than in the warfarin group (0,5% vs. 0,7% per year). However major bleeding from a gastrointestinal site was more common in the rivaroxaban group (3,2%), as compared with warfarin group (2,2%).

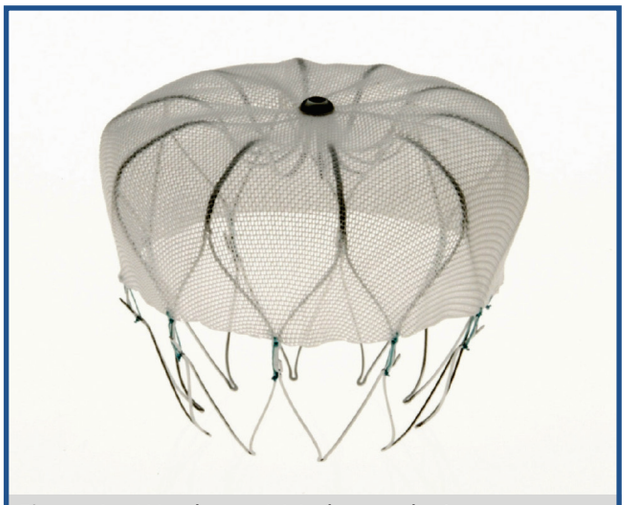


Figure 1a. Watchman LAA closure device system components.
Frame: Nitinol structure
Available sizes:
21, 24, 27, 30, 33 mm (diameter)
10 Fixation anchors around device perimeter engage LAA tissue
Contour shape accommodates most LAA anatomy
Fabric Cap: (PET) Fabric Polyethyl terephthalate
Prevents harmful emboli from exiting during the healing process
160 micron filter

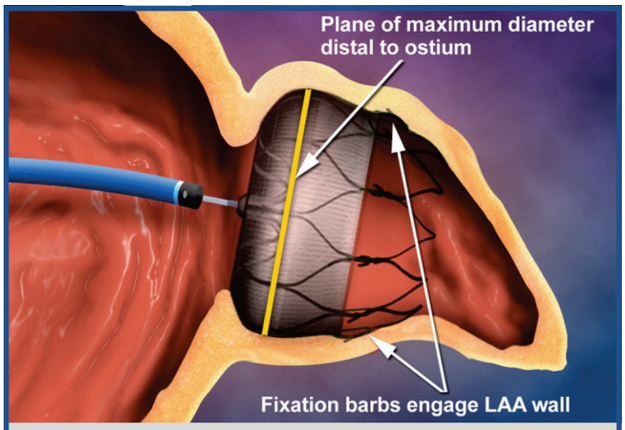


Figure 1b. Optimal position of Watchman device during deployment.

Left atrial appendage closure as alternative to pharmacological therapy

Though there are several pharmacological antithrombotic possibilities, some groups of patients with several contraindications, especially high risk of bleeding and with history of bleeding complications, cannot be offered any of them. Therefore, LAA closure may be an attractive alternative. Attempts to decrease risk of LAA thrombus embolisms resulted in development of surgical excision and percutaneous LAA occlusion techniques. James Cox[7], on the basis of surgical studies and his own observations, concludes that removal or proper closure of the LAA at surgery reduces the risk of perioperative and long-term stroke. According to current guidelines[3] LAA surgical excision may be considered in patients undergoing open heart surgery (IIb C). Interventional percutaneous LAA closure may be considered in patients with a high stroke risk and contraindications for long-term oral anticoagulation. The LAA closure devices are designed to seal the neck of LAA and reduce thrombus embolization[20].

Currently, two LAA closure devices are available for clinical use – Watchman™ left atrial appendage closure device (Watchman device) (Boston Scientific) and Amplatzer™ Cardiac Plug (Amplatzer device) (St. Jude Medical).

The Watchman device was introduced in 2005. It was designed to be permanently implanted at or slightly distal to the ostium of LAA to trap thrombus before it exits the LAA. The Watchman LAA Closure Technology consists of the Watchman transseptal access system, delivery catheter and an implantable device. The Watchman device is a self-expanding nitinol frame

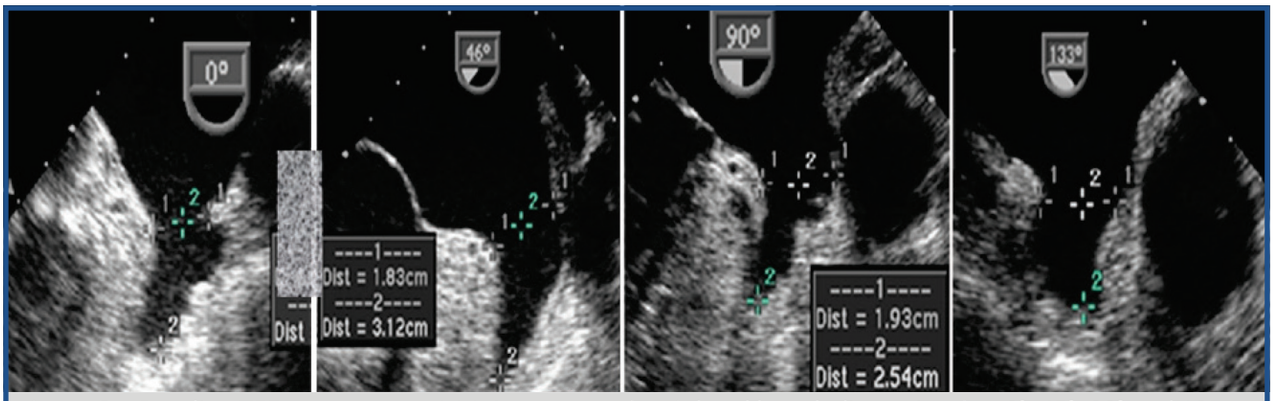


Figure-2a. Baseline TEE assessment - *LAA Assessment (ostial and length dimensions) at 0^0, 45^0, 90^0 and 135^o.*

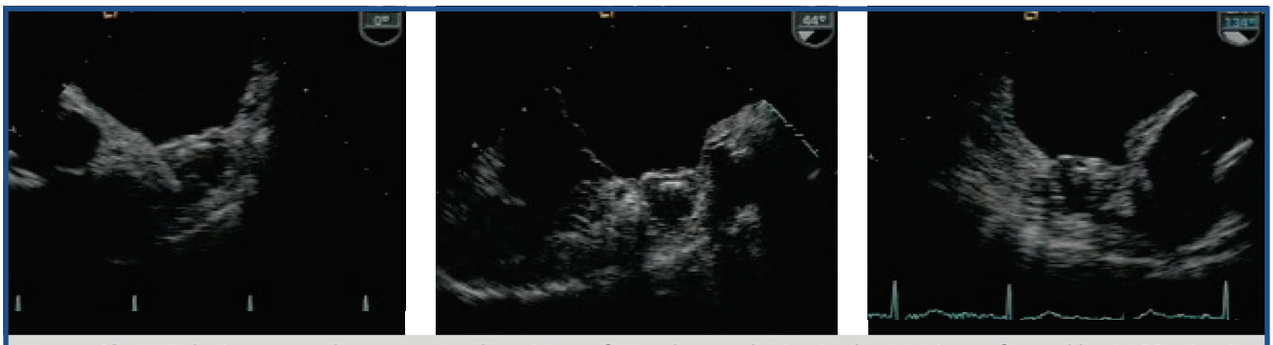


Figure-2b. TEE during procedure – optimal position of Watchman device in the LAA is confirmed by PASS criteria:

1. device is distal to or at the ostium of the LAA;
2. fixation anchors are engaged an device is stable;
3. device is compressed at least 8-20% of original size;
4. device spans ostium, all lobes of LAA are covered (no residual flow noted around device).

structure with fixation barbs and a permeable polyester fabric cover (Fig-1a and Fig-1b). It is available in 5 sizes (21-33mm) and is preloaded within a delivery catheter.

Several studies have shown the feasibility of percutaneous LAA occlusion[20-25]. The first randomized study, the Percutaneous Closure of the Left Atrial Appendage versus Warfarin Therapy for Prevention of Stroke in Patients with Atrial Fibrillation (PROTECT-AF) trail[22], evaluated the efficacy and safety of the Watchman device compared with standard warfarin therapy. The trial revealed that the efficacy of percutaneous closure of the LAA with the Watchman device is non-inferior to ongoing warfarin therapy with regard to prevention of stroke, systemic embolism, and cardiovascular death. Moreover, the newest analysis of 5 year follow-up of the PROTECT–AF trial revealed significant reduction in cardiovascular (60%) and all-cause mortality (34%) in patients treated with the Watchman device compared with warfarin group[26].

The data from the PROTECT-AF study were confirmed by CAP Registry[27] and PREVAIL study[28] which also showed decreased procedure time, improved implant success and procedure/device related safety with increased operator experience. It must be pointed out that these 3 studies were performed in patients who were eligible to take warfarin.

The ASAP study[29] evaluated the safety and feasibility of the Watchman device for the treatment of non-valvular atrial fibrillation in patients with a contraindication to warfarin. The study showed that Watchman implantation for warfarin contraindicated AF patients is feasible, associated with low, but manageable, rate of device thrombus and decreases the rate of stroke by 77%.

The U.S. Food and Drug Administration (FDA) Circulatory System Devices Panel of the Medical Devices Advisory Committee voted on Dec. 11, 2013 favourably by a majority (13 to 1) that the benefits of the WATCHMAN Left Atrial Appendage Closure device outweigh the risks, there is a reasonable assurance that the device is safe and of a reasonable assurance of efficacy. The final decision and approval from the FDA is expected in the first half of 2014 and this innovative technology will be available to patients with AF at higher risk for stroke who need an alternative to long-term warfarin therapy also in USA.

The data regarding the clinical usage of the Amplatzer Cardiac Plug are based on reports of single-centre experience and registries[23,25]. Up to now there are no randomized trials comparing Amplatzer device with oral anticoagulants, thus, in authors opinion, their usage should be for now limited to clinical trials.

Left atrial appendage closure procedure with the Watchman device

The procedures may be done under general (preferably) or local anesthesia and with the use of transoesophageal echocardiography and fluoroscopy in a

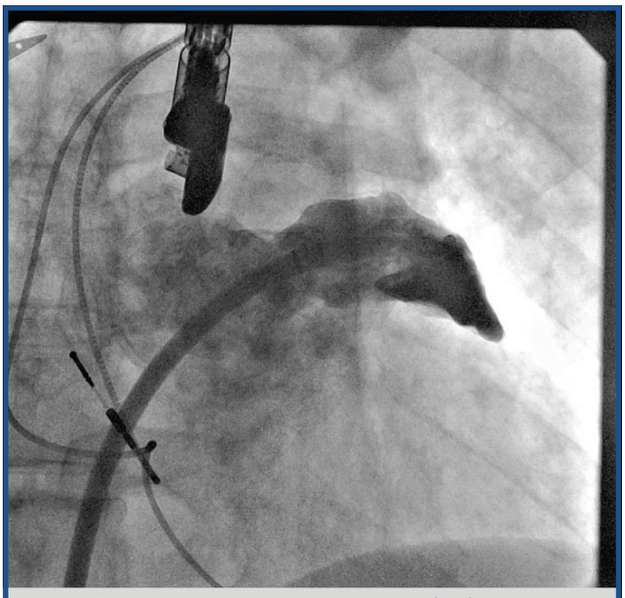


Figure 3a. Fluroscopic visualization of left atrial appendage and right atrium through guiding catheter located in the ostium of left atrial appendage

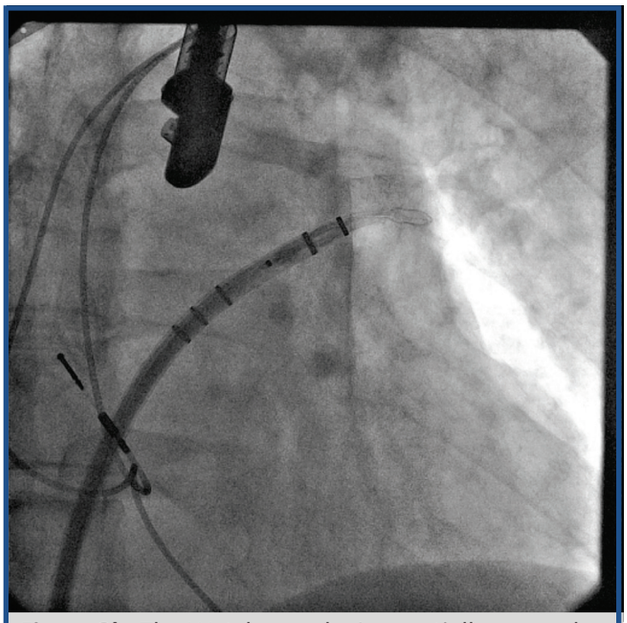


Figure 3b. The Watchman device partially opened in the left atrial appendage

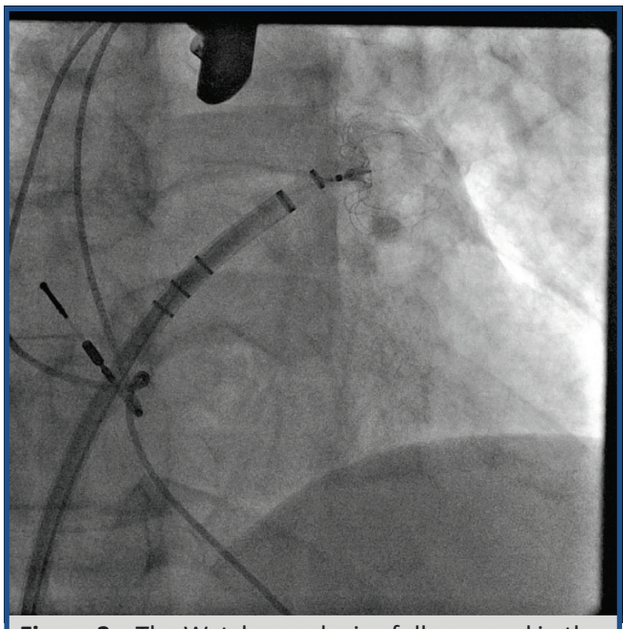


Figure 3c. The Watchman device fully opened in the left atrial appendage

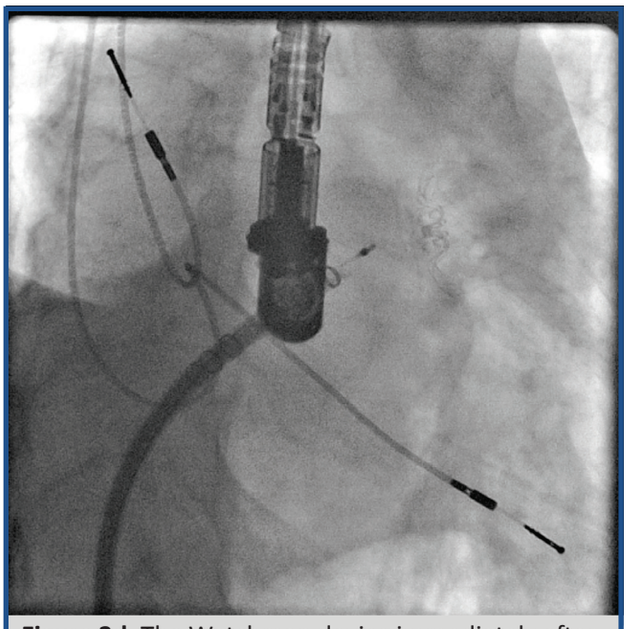


Figure 3d. The Watchman device immediately after release from delivery cable

catheterization laboratory (Fig. 2a-2b; Fig 3a-3d). Vascular access is obtained with puncture of femoral vein. After cannulation of the femoral vein, a mid-low and posterior transseptal puncture is performed under transoesophageal echocardiography guidance using conventional transeptal needle and delivery sheat. Heparin is then given to keep an ACT above 250 sec. Then, the Watchman Access Sheath and Dilator are advanced over a guidewire into the left atrium. The LAA is engaged with a 5F-6F pigtail catheter to perform selective angiograms. The Access Sheath is then carefully advanced into the distal portion of the LAA over a pigtail catheter. The LAA morphology is then carefully analysed in both angiograms and transoesophageal echocardiography to determine which size of the Watchman device should be implanted. Precise measurements of LAA are carried out in transoesophageal echocardiography in 0, 45, 90 and 135 degree. The Watchman Delivery System is prepared, inserted into the Access Sheath, and slowly advanced under fluoroscopic guidance. The Watchman Device is then deployed into the LAA. The device release criteria are confirmed via fluoroscopy and TEE prior to releasing the device.

Periprocedural complications are the major problem of interventional LAA closure, especially during learning phase. The overall complication rate could be as high as 8,7-11,7%.[20,22,27,29] Most often are pericardial effusion (1,1-5,0%), cardiac tamponade (1,1-1,3%), major blee-

ding (3,5%), puncture site complications (2%), thrombus formation on the device (0,7-1,1%) or on the sheath (0,6%), device embolization (0,6-1,7%), air embolization (1,7%), ischemic stroke (0,7-1,1%) or hemorrhagic stroke (0,2%) or TIA (0,6%).[20,22,27,29] In PROTECT-AF trial[22] twenty one of 463 subjects assigned to the intervention group died during the study, however no deaths were deemed related to the Watchman device. Similarly no deaths device or procedure related were reported in the ASAP study[29] and in Matsuo el al. study[20]. According to results of CAP and PREVAIL[27, 28] there is a significant improvement in the safety of Watchman left atrial appendage closure with increased operator experience. In the study performed by Reddy et al.[27] the cohort included 542 patients of the PROTECT-AF trial and a subsequent registry of 460 patients undergoing Watchman implantation (Continued Access Protocol - CAP Registry). A remarkable reduction in the rate of procedure- or device-related safety events was observed, including reduction in procedural time (mean 62±34minutes in PROTECT-AF and mean 50±21minutes in CAP), the rate of serious pericardial effusion (5% in PROTECT-AF to 2,2% in CAP), device embolization (3 cases in PROTECT-AF and none in CAP), and periprocedural stroke rates (0,9% in PROTECT-AF and no strokes in CAP). The successfulness of implantation increased from 89,5% in PROTECT-AF to 95% in CAP. Pericardial effusion was the major component of early safety events in PROTECT-AF. Based on the review of procedural details, fluoroscopy and TEE imaging, a variety of causes of pericardial effusion were recognized, ranging from being the result of transseptal puncture, the delivery sheath, or the actual manipulation of the Watchman device itself. The rate of serious pericardial effusion in CAP was less than half that seen in PROTECT-AF. There was also experience-related improvement in periprocedural stroke rate. This complication was largely related to the inadvertent introduction of air entrapped within the sheath to the systemic circulation during the procedure. With careful sheath management, there have been no periprocedural strokes in the CAP registry. Similarly, procedural protocol changes implemented over the study period, resulted in decrease in device embolization rate. Importantly, the safety events rates in the Watchman group had a skewed distribution with a large initial event rate, and subsequent rate during follow-up, while the safety events in the warfarin group occurred at approximately constant rates over time and would be expected to continue to accumulate linearly potentially beyond the end of the study period[27]. Not surprisingly, in Reddy et al.[24] analysis the exclusion of periprocedural adverse events favored the device strategy. After exclusion of events that occurred on the day of device deployment, fewer patients experienced the primary efficacy events in device than in the control warfarin group (postprocedure, 2,5% per year versus 4,3% per year). The similar result was found when analysis was confined to patients who stopped warfarin after successful device deployment (2,3% per year versus 4,1% per year), as well as those who completed therapy with warfarin and clopidogrel and were only taking aspirin (2,3% per year versus 4,1% per year in control group). These analyses suggest that after successful procedure, the LAA device is more effective than continued warfarin therapy.

Post-interventional anti-thrombotic treatment schedule is not clearly established yet. PROTECT-AF [22] patients were treated with warfarin for 45 days to facilitate device endothelialisation. Warfarin was then stopped depending on the result of the transoesophageal echocardiography 45 days after the procedure (lack of flow around the device) and pharmacotherapy was continued with clopidogrel 75 mg daily for 6 months and aspirin (81–325 mg daily) for long term use. The non-randomised ASAP study29] showed that treatment with aspirin and clopidogrel in patients with contraindications for even short term anticoagulation is feasible, safe and effective.

Conclusions

The clinical data demonstrate that the WATCHMAN LAA Closure Technology is a safe and effective alternative to warfarin therapy in reducing the risk of stroke, cardiovascular death and systemic thromboembolism in patients with non-valvular atrial fibrillation. It should be especially strongly considered in patients who have contraindications for oral anticoagulation or have complications associated with such treatment.

References:

1. Go AS, Hylek EM, Phillips KA et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. JAMA 2001; 285: 2370-2375.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991; 22: 983-988.
3. Camm AJ, Lip GY, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 2012; 33: 2719-2747.
4. Steger C, Pratter A, Martinek-Bregel M, et al. Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian Stroke registry. Eur Heart J 2004; 25: 1734-1740.
5. Lamassa M, Di Carlo A, Pracucci G, et al. Characteristics, outcome, and care of stroke associated with atrial fibrillation in Europe: data from a multicenter multinational hospital-based registry (The European Community Stroke Project). Stroke 2001; 32:392-398.
6. Blackshear JL, Odell JA. Appendage obliteration to reduce stroke in cardiac surgical patients with atrial fibrillation. Ann Thorac Surg 1996; 61:755-759.
7. Cox JL. Mechanical closure of the left atrial appendage: is it time to be more aggressive? J Thorac Cardiovasc Surg 2013; 146: 1018-1027.e2.
8. Crystal E, Connolly SJ. Role of oral anticoagulation in management of atrial fibrillation. Heart 2004; 90: 813-817.
9. Al-Saady NM, Obel OA, Camm AJ. Left atrial appendage: structure, function, and role in thromboembolism. Heart 1999; 82:547-554.
10. Chatterjee S, Alexander JC, Pearson PJ, Feldman T. Left atrial appendage occlusion: lessons learned from surgical and transcatheter experiences. Ann Thorac Surg 2011; 92: 2283-2292.
11. Stöllberger C, Schneider B, Finsterer J. Elimination of the left atrial appendage to prevent stroke or embolism? Anatomic, physiologic, and pathophysiologic considerations. Chest 2003; 124: 2356-2362.

12. Omari BO, Nelson RJ, Robertson JM. Effect of right atrial appendectomy on the release of atrial natriuretic hormone. J Thorac Cardiovasc Surg 1991; 102: 272-279.
13. Kim KB, Lee CH, Kim CH, Cha YJ. Effect of the Cox maze procedure on the secretion of atrial natriuretic peptide. J Thorac Cardiovasc Surg 1998; 115: 139-146.
14. Yoshihara F, Nishikimi T, Sasako Y, et al. Preservation of the right atrial appendage improves reduced plasma atrial natriuretic peptide levels after the maze procedure. J Thorac Cardiovasc Surg 2000; 119: 790-794.
15. Wyse DG, Waldo AL, DiMarco JP, et al. Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347: 1825-1833.
16. Nieuwlaat R, Olsson SB, Lip GY, et al.; Euro Heart Survey Investigators. Guideline-adherent antithrombotic treatment is associated with improved outcomes compared with undertreatment in high-risk patients with atrial fibrillation. The Euro Heart Survey on Atrial Fibrillation. Am Heart J 2007; 153:1006-1012.
17. Ogilvie IM, Newton N, Welner SA, Cowell W, Lip GY. Underuse of oral anticoagulants in atrial fibrillation: a systematic review. Am J Med 2010; 123:638-645.e4.
18. Connolly SJ, Ezekowitz MD, Yusuf S, et al.; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361:1139-1151.
19. Patel MR, Mahaffey KW, Garg J, et al.; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365:883-891.
20. Matsuo Y1, Sandri M, Mangner N, et al. Interventional closure of the left atrial appendage for stroke prevention. Circ J 2014; 78: 619-624.
21. Bayard YL, Omran H, Neuzil P, et al. PLAATO (Percutaneous Left Atrial Appendage Transcatheter Occlusion) for prevention of cardioembolic stroke in non-anticoagulation eligible atrial fibrillation patients: results from the European PLAATO study. EuroIntervention 2010; 6: 220-226.
22. Holmes DR, Reddy VY, Turi ZG, et al.; PROTECT AF Investigators. Percutaneous closure of the left atrial appendage versus warfarin therapy for prevention of stroke in patients with atrial fibrillation: a randomised non-inferiority trial. Lancet 2009; 374:534-542.
23. Streb W, Szymała M, Kukulski T, et al. Percutaneous closure of the left atrial appendage using the Amplatzer Cardiac Plug in patients with atrial fibrillation: evaluation of safety and feasibility. Kardiol Pol. 2013;71(1):8-16.
24. Reddy VY, Doshi SK, Sievert H, et al.; PROTECT AF Investigators. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. Circulation 2013; 127:720-729.
25. Lam YY, Yip GW, Yu CM, et al. Left atrial appendage closure with AMPLATZER cardiac plug for stroke prevention in atrial fibrillation: initial Asia-Pacific experience. Catheter Cardiovasc Interv 2012; 79:794-800.
26. Long Term Results of PROTECT AF: The Mortality Effects of Left Atrial Appendage Closure Versus Warfarin for Stroke Prophylaxis in AF - Dr Vivek Y Reddy (Mount Sinai School of Medicine, New York, NY) when presenting the data at the Heart Rhythm Society 2013 Scientific Sessions.
27. Reddy VY, Holmes D, Doshi SK, Neuzil P, Kar S. Safety of percutaneous left atrial appendage closure: results from the Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF (PROTECT AF) clinical trial and the Continued Access Registry. Circulation 2011; 123:417-424.
28. http://www.bostonscientific.com/watchman-eu/clinical-data/prevail-clinical-study.html
29. Reddy VY, Möbius-Winkler S, Miller MA, et al. Left atrial appendage closure with the Watchman device in patients with a contraindication for oral anticoagulation: the ASAP study (ASA Plavix Feasibility Study With Watchman Left Atrial Appendage Closure Technology). J Am Coll Cardiol 2013; 61: 2551-2556.

Srce i krvni sudovi 2014; 33(1): 41-43

Pregledni rad

The current status of drug-coated balloons in in-stent restenosis treatment

Leszek Bryniarski, Łukasz Klima, Sławomir Surowiec

Department of Cardiology, Interventional Electrophysiology and Hypertension, University Hospital, Jagiellonian University Medical College, Kraków, Poland

Abstract Restenosis after angioplasty has always been a significant problem in interventional cardiology and is associated with significant morbidity and costs, with a wide spectrum of clinical presentation. The population treated with bare metal stents and drug eluting stents is very large and because of the complex subset of patients and lesions the overall rate of in-stent restenosis remains significant. For interventional cardiologist several treatment options are available nowadays such as repeat stenting, balloon angioplasty, drug-coated balloons but due to lack of precise guidelines the management remains challenging. In this paper authors provide comprehensive review of novel technique in in stent restenosis treatment: drug eluting balloons.

Key words in-stent restenosis, drug eluting balloons, drug coated balloons.

Introduction

Percutaneus coronary interventions (PCI) has evolved to the mainstream revascularization method far outnumbering coronary artery bypass grafting (CABG). However, the major drawback of PCI is a higher rate of target lesion revascularization (TLR) in comparison to CABG due to in-stent restenosis. Restenosis after angioplasty has always been a significant problem in interventional cardiology and is associated with significant morbidity and costs, with a wide spectrum of clinical presentation. The disadvantages of balloon angioplasty has been removed when bare metal stents (BMS) were invented. The introduction of these devices significantly reduced restenosis after angioplasty. Development of drug eluting stents (DES) an another milestone in treatment of patients with coronary artery disease. The high efficacy of these devices in prevention of restenosis compared with bare metal stents has allowed percutaneus coronary intervention to be used in complex lesions. Introduction of DES reduced the number of target lesion revascularizations but did not eliminate the in-stent restenosis (ISR). The population treated with BMS and DES is very large[1] and because of the complex subset of patients and lesions the overall rate of ISR remains significant. Although several treatment options are available nowadays such as repeat stenting, balloon angioplasty (BA), drug-coated balloons (DCB) there it is always a dilemma for interventional cardiologist which devices to use, so management remains challenging. We provide comprehensive review of novel technique in ISR treatment: drug eluting balloons (DEBs).

Definition

Restenosis is defined as reduction of ≥50% of lumen diameter after PCI at follow-up angiography. Although this definition was used as end point in large number of clinical trials it has to be emphasized that apart from angiographic findings clinical manifestation of ischemia plays significant role in decision of treatment.

Pathophysiology

After stent implantation, which damages the endothelium and leads to regional and systemic inflammatory reaction, process of neointima proliferation begins and in months leads to neointimal hyperplasia[2]. Stent underexpansion or not optimal atherosclerotic plaque coverage with stent favors ISR. But according to the latest findings it seems that one more factor is responsible for ISR, especially in late stage - neoatherosclerosis[3]. What is interesting novel atherosclerotic plaques are formed faster in drug eluting stent (after one year) than in bare metal stent (after four years). Detailed description of pathophysiology of ISR is will not be the subjects of this paper. Type of ISR and cause of its occurrence determines its treatment.

Treatment

When treating ISR we should take several possibilities into consideration and these are: optimal medical therapy (OMT),balloon angioplasty, stenting (BMS, the same DES, different DES), DEB and cardiac surgery. In first human trial on DEB - a PACCOCATH ISR I/II patients with BMS-ISR were randomized to Paccocath DEB versus standard balloon angioplasty. After 6 months major cardiac

events (MACE) appeared in 4% in DEB arm and 31% in BA group[4]. After 24 months observation MACE rated 11% vs 46% and target lesion revascularization (TLR) 6% and 37% respectively in DEB and BA arm[5]. In other trial on drug-coated balloons use of DEB resulted in smaller late lumen loss (LLL) in BMS restenosis to compare with DES restenosis (-0,05 vs 0,19 mm respectively) what reflected in fewer revascularizations at one year (2.4 vs 17.1% respectively)[6]. Similarly, both the Spanish DIOR and the SeQuent Please registries[7, 8] highlighted better clinical outcomes with BMS ISR compared to DES ISR. However, outcomes of paclitaxel versus non-paclitaxel DES ISR treated with Sequent Please did not differ (TLR: 8.3% versus 10.8%; P=0.46). Perhaps the efficacy of drug coated balloons in treating BMS ISR reflects the fact that a drug is introduced for the first time, whereas DCB is less efficacious in a 'drug-resistant' vessel manifesting DES ISR. Another reason could be that drug eluting stents are implanted in complex lesions which predisposes to restenosis. Comparison of drug-coated balloons with drug eluting stents (SeQuent Please, B. Braun versus TAXUS stent by Boston Scientific) in management of in-BMS restenosis was analyzed in PEPCAD II trial which demonstrated non-inferiority. After 6 months of follow up late lumen loss was estimated as 0,38±0,61 mm in DES and 0,17±0,42 mm in DEB (P=0,03) and binary restenosis respectively 20% i 7% (P=0,03). After 12 months of observation MACE appeared in 22% in DES and 9% in DEB group (P=0,08)[9]. In recently published German consensus on drug-coated balloon [10] authors suggest to treat BMS in-stent restenosis with drug-coated balloons leaving DES as a bailout therapy when dissection after predilatation appears with TIMI flow < III or when residual stenosis exceeds 30%. The used DEB should extend 2-3 mm beyond the pre-dilated area, balloon/vessel ratio should equal 0.8-1.0 and pressure 8-10 atm, whereas time of inflation must not be shorter than 30 second. The authors suggest predilatation with conventional balloon not longer than stent if ISR is restricted to stent, with diameter approximately 0.5 mm smaller than vessel diameter and with nominal pressure. Second conventional balloon should be shorter than stent with balloon to vessel diameter ratio 0.8-1.0 and inflated with pressure 12-16 atm. The European guidelines give DEB class IIa and level of evidence B in bare metal stent restenosis treatment[11].

In DES ISR situation is more complicated and there is now clear evidence what kind of management gives the best results. There is evidence that implantation of another DES is better than BA[12]. ISAR DESIRE 2 study was designed to answer the question whether we should use stent eluting the same or alternative drug. There was no difference between sirolimus eluting stent (SES) or paclitaxel eluting stent (PES) in LLL, TLR or binary restenosis[13]. In other trial, PEPCAD-DES[14], where DEB and BA in treatment DES ISR were compared the TLR and MACE rated significantly lower in group of drug-coated balloon (16.7% vs 50% and 15.3% vs 36,8% respectively). The treatment with DEB resulted with significantly lower LLL (0.43 versus 1.03 mm) and restenosis (17.2% versus 58.1%). Finally in recent ISAR DESIRE 3 study[15] the comparison of all three methods (BA, DEB, DES) in treatment of DES in-stent restenosis was made. There was no difference between diameter stenosis between DEB and DES (38% and 37.4% respectively) and both methods were superior to BA (54.1%). In terms of binary stenosis DEB and DES were comparable (26.5% and 24.0%) and superior to BA (56.7%). As for TLR in DEB 22.1%, in DES 13.5% (P=0.09), in BA 43.5%. That led authors to conclusion that in patients presenting with 'limus'-DES restenosis, DEB therapy is non-inferior to repeat stenting with PES. Both DEB and PES therapy are superior to balloon angioplasty alone.

It may seem counterintuitive that short balloon inflation with DEB can be superior to DES which have a longer duration of drug but delivery there are several theoretical advantages of DEB:

- avoiding the problem of permanent implant causing inflammation and hypersensitivity reaction
- delivery of antiproliferative medication when needed, for instance immediately after the barotraumas induced by balloon angioplasty
- avoiding multiple layers of stent
- avoiding the potential risk of corrosion of the stent: the mechanical friction between overlapping stents and chemical reactions between dissimilar alloys if mixing different stent types could lead to corrosion. Stent alloys form a protective oxide film, insulating the stent struts from the corrosive body fluids. There is a risk of mechanical damage of the oxide film caused micromotion at point of stent overlap. If this protective film is getting scratched off by overlapping stent struts the underlying stent struts get exposed and may undergo corrosion.
- overlapping stents of different alloys could theoretically lead to galvanic corrosion. This can be avoided by DEB. However, these concerns are rather theoretical, there is no clinical evidence which indicates a problem of using different types of overlapping stents[16].

Conclusion

By obviating the need for additional stent implantation treatment with a drug-eluting balloon may be the treatment of choice in patients presenting with 'limus'-DES restenosis. In bare metal stent restenosis the drug-coated balloon should be the golden standard therapy leaving DES implantation only as bailout therapy. Balloon angioplasty can be successfully used when stent underexpansion diagnosed with IVUS is cause of ISR and when dealing with focal restenosis.

References

1. Cutlip DE, Chauhan MS, Baim DS, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. J Am Coll Cardiol 2002; 40(12):2082-9.
2. Dangas GD, Claessen BE, Caixeta A, et al. In-stent restenosis in the drug-eluting stent era. J Am Coll Cardiol 2010; 56(23): 1897-907.
3. Park SJ, Kang SJ, Virmani R, et al. In-stent neoatherosclerosis: a final common pathway of late stent failure. J Am Coll Cardiol 2012; 59(23): 2051-7.
4. Scheller B, Hehrlein C, Bocksch W, et al. Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. N Engl J Med 2006; 355(20): 2113-24.

5. Scheller B, Hehrlein C, Bocksch W, et al. Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. Clin Res Cardiol 2008; 97(10): 773-81.
6. Hehrlein C, Dietz U, Kubica J, et al. Twelve-month results of a paclitaxel releasing balloon in patients presenting with in-stent restenosis First-in-Man (PEPPER) trial. Cardiovasc Revasc Med 2012; 13(5): 260-4.
7. Wohrle J, Zadura M, Mobius-Winkler S, et al. SeQuentPlease World Wide Registry: clinical results of SeQuent please paclitaxel-coated balloon angioplasty in a large-scale, prospective registry study. J Am Coll Cardiol 2012; 60(18): 1733-8.
8. Vaquerizo B, Serra A, Miranda-Guardiola F, et al. One-year outcomes with angiographic follow-up of paclitaxel-eluting balloon for the treatment of in-stent restenosis: insights from Spanish multicenter registry. J Interv Cardiol 2011; 24(6): 518-28.
9. Rosenkranz S, Maier LS, Maack C, et al. Hotline update of clinical trials and registries presented at the German Cardiac Society Meeting 2007: 2L-Registry, Kardio-Pro, EVER, AFFECT, VTACH, ARTS II, OPTAMI, PEPCAD I, PEPCAD II, GERSHWIN, SPICE, FIX-CHF and CREDIT. Clin Res Cardiol 2007; 96(7): 457-68.
10. Kleber FX, Mathey DG, Rittger H, et al. How to use the drug-eluting balloon: recommendations by the German consensus group. EuroIntervention 2011; 7 Suppl K: K125-8.
11. Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J 2010; 31(20): 2501-55.
12. Song HG, Park, DW, Kim YH, et al. Randomized trial of optimal treatment strategies for in-stent restenosis after drug-eluting stent implantation. J Am Coll Cardiol 2012; 59(12): 1093-100.
13. Mehilli J, Byrne RA, Tiroch K, et al. Randomized trial of paclitaxel-versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. J Am Coll Cardiol 2010; 55(24): 2710-6.
14. Rittger H, Brachmann J, Sinha AM, et al. A randomized, multicenter, single-blinded trial comparing paclitaxel-coated balloon angioplasty with plain balloon angioplasty in drug-eluting stent restenosis: the PEPCAD-DES study. J Am Coll Cardiol 2012; 59(15): 1377-82.
15. Byrne RA, Neumann FJ, Mehilli J, et al. Paclitaxel-eluting balloons, paclitaxel-eluting stents, and balloon angioplasty in patients with restenosis after implantation of a drug-eluting stent (ISAR-DESIRE 3): a randomised, open-label trial. Lancet 2013; 381(9865): 461-7.
16. Indermuehle A, Bahl R, Lansky AJ, et al. Drug-eluting balloon angioplasty for in-stent restenosis: a systematic review and meta-analysis of randomised controlled trials. Heart 2013; 99(5): 327-33.

Srce i krvni sudovi 2014; 33(1):44-86

Preporuke za dijagnostiku i lečenje valvularnih bolesti srca (2012)

Zajednička radna grupa za vođenje valvularne bolesti srca Evropskog udruženja kardiologa (ESC) i Evropskog udruženja kardio-torakalnih hirurga (EACTS)

Eur Heart 2012;33:2451-2496
doi:10.1093/eurheartj/ehs109

Guidelines on the management of valvular heart disease (version 2012)

The Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)

Authors/Task Force Members: Alec Vahanian (Chairperson) (France)*, Ottavio Alfieri (Chairperson)* (Italy), Felicita Andreotti (Italy), Manuel J. Antunes (Portugal), Gonzalo Barón-Esquivias (Spain), Helmut Baumgartner (Germany), Michael Andrew Borger (Germany), Thierry P. Carrel (Switzerland), Michele DeBonis (Italy), Arturo Evangelista (Spain), VoLVmar FaLV (Switzerland), Bernard Iung (France), Patrizio Lancellotti (Belgium), Luc Pierard (Belgium), Susanna Price (UK), Hans-Joachim Schäfers (Germany), Gerhard Schuler (Germany), Janina Stepinska (Poland), Karl Swedberg (Sweden), Johanna Takkenberg (The Netherlands), Ulrich Otto Von Oppell (UK), Stephan Windecker (Switzerland), Jose Luis Zamorano (Spain), Marian Zembala (Poland)
ESC Committee for Practice Guidelines (CPG): Jeroen J. Bax (Chairperson) (The Netherlands), Helmut Baumgartner (Germany), Claudio Ceconi (Italy), Veronica Dean (France), Christi Deaton (UK), Robert Fagard (Belgium), Christian Funck-Brentano (France), David Hasdai (Israel), Arno Hoes (The Netherlands), Paulus Kirchhof (United Kingdom), Juhani Knuuti (Finland), Philippe Kolh (Belgium), Theresa McDonagh (UK), Cyril Moulin (France), Bogdan A. Popescu (Romania), Željko Reiner (Croatia), Udo Sechtem (Germany), Per Anton Sirnes (Norway), Michal Tendera (Poland), Adam Torbicki (Poland), Alec Vahanian (France), Stephan Windecker (Switzerland)
Document Reviewers:: Bogdan A. Popescu (ESC CPG Review Coordinator) (Romania), Ludwig Von Segesser (EACTS Review Coordinator) (Switzerland), Luigi P. Badano (Italy), Matjaž Bunc (Slovenia), Marc J. Claeys (Belgium), Niksa Drinkovic (Croatia), Gerasimos Filippatos (Greece), Gilbert Habib (France), A. Pieter Kappetein (The Netherlands), Roland Kassab (Lebanon), Gregory Y.H. Lip (UK), Neil Moat (UK), Georg Nickenig (Germany), Catherine M. Otto (USA), John Pepper, (UK), Nicolo Piazza (Germany), Petronella G. Pieper (The Netherlands), Raphael Rosenhek (Austria), Naltin Shuka (Albania), Ehud Schwammenthal (Israel), Juerg Schwitter (Switzerland), Pilar Tornos Mas (Spain), Pedro T. Trindade (Switzerland), Thomas Walther (Germany)
The disclosure forms of the authors and reviewers are available on the ESC website www.escardio.org/guidelines

Sadržaj

Prevod ESC preporuka: Olga Petrović, Klinika za kardiologiju, Klinički centar Srbije, Višegradska 26, Beograd
Stručni konsultant za prevod: Bosiljka Vujisić Tešić, Klinika za kardiologiju, Klinički centar Srbije, Višegradska 26, Beograd

Skraćenice i akronimi

ACE angiotensin-konvertujući enzim
AF atrialna fibrilacija
aPTT aktivirano parcijalno tromboplastinsko vreme
AR aortna regurgitacija
ARB blokatori receptora angiotenzina
AS aortna stenoza
B zamena aortne valvule
BNP B-tip natriuretskog peptida
BSA površina tela
CABG koronarni bajpas
CAD koronarna bolest
CMR srčana magnetna rezonanca
CPG Komitet za preporuke
CRT srčana resinhronizaciona therapija
CT kompjuterizovana tomografija
EACTS Evropsko udruženje kardio-torakalnih hirurga
EKG elektrokardiogram
EF ejektiona frakcija
EROA efektivna veličina regurgitirajućeg otvora
ESC Evropsko udruženje kardiologa
EVEREST (Endovascular Valve Edge-to-Edge REpair STudy)
SI srčana insuficijencija
INR internacionalni normalizovani odnos
LA leva pretkomora
LMWH niskomolekularni heparin
LV leva komora
LVEF ejekciona frakcija leve komore
LVEDD enddijastolni dijametar leve komore
LVESD endsistolni dijametar leve komore
MR mitralna regurgitacija
MS mitralna stenoza
MSCT multi slajs kompjuterizovana tomografija
NYHA Njujorška srčana asocijacija
PISA proksimalna izobrzinska površina
PMC perkutna mitralna komisurotomija
PVL paravalvularno curenje
RV desna komora
rtPA rekombinovani tkivni plazminogen aktivator
SVD strukturno valvularno oštećenje
STS Udruženje torakalnih hirurga
TAPSE tricuspid annular plane systolic excursion
TAVI transkateterska implantacija aortne valvule
TEE transezofagusna ehokardiografija
TR trikuspidna regurgitacija
TS trikuspidna stenoza
TTE transtoraksna ehokardiografija
UFH nefrakcionirani heparin
VHD valvularna bolest srca
3DE trodimenzionalna ehokardiografija

1. Predgovor

Preporuke rezimiraju i procenjuju sve raspoložive dokaze u vreme njihovog nastanka sa ciljem da pomognu lekarima u izboru najbolje strategije lečenja za svakog pojedinačnog bolesnika sa navedenim stanjem uzimajući u obzir uticaj na ishod, kao i odnos rizik, korist za svaku pojedinačnu dijagnostičku ili terapijsku proceduru. Preporuke nisu zamena nego dodatak udžbenicima i obuhvataju poglavlja iz ESC Heart Curiculuma. Preporuke treba da pomognu lekarima kod donošenja odluka u svakodnevnoj praksi. Ipak, konačnu odluku u vezi sa bolesnikom treba da donese nadležni lekar.

Poslednjih godina veliki broj preporuka je izdat od strane Evropskog udruženja kardiologa i drugih udruženja i organizaciija. Zbog uticaja na kliničku praksu ustanovljeni su kriterijumi kvaliteta da bi sve odluke bile jasne korisniku. Preporuke za formulisanje i izdavanje ESC preporuka mogu se naći na sledećem web sajtu (http://www.escardio.org/guidelines-surveys/esc-guidelines/about/Pages/rules-writing.aspx). Preporuke ESC predstavljaju zvaničan stav ESC o datoj temi i redovno se osavremenjuju.

Članovi radne grupe se biraju od strane ESC i Evropske asocijacije za kardiotorakalnu hirurgiju (EACTS) i predstavljaju profesionalce uključene u brigu o bolesnicima sa ovom patologijom. Izabrani stručnjaci iz ove oblasti preduzeli su sveobuhvatan pregled objavljenih dokaza za dijagnostiku, lečenje i/ili sprečavanje datog stanja, u skladu sa ESC odborom za praktične vodiče (CPG) i EACTS. Izvršena je kritička procena dijagnostičkih i terapijskih procedura, uključujući procenu odnosa i koristi rizika. Procene očekivanih zdravstvenih ishoda za veće populacije su bile uključene, tamo gde podaci postoje. Nivoi dokaza i snaga preporuka pojedinih mogućnosti lečenja su procenjeni i ocenjeni prema unapred definisanim skalama, kao što je navedeno u tabelama 1 i 2. Stručnjaci koji su pisali i razmatrali panele popunili su izveštaje o aktivnostima koje bi mogle biti uočene kao stvarni ili potencijalni izvori sukoba interesa. Ovi izveštaji su objedinjeni u jedan fajl koji se može naći na ESC veb sajtu (http://vvv.escardio.org/guidelines). Bilo kakve promene u izjavama o svojim interesima koji se javljaju u toku pisanja moraju se ažurirati. Radna grupa ima podršku od ESC i EASC bez uključivanja zdravstvene industrije.

ESC CPG nadzire i koordiniše pripremu novih Vodiča od strane Radne grupe, ekspertske grupe ili saglasnih odbora. Odbor je takođe odgovoran za odobravanje ovih Vodiča. ESC Vodiči podležu opširnoj reviziji CPG i spoljnih eksperata. Nakon adekvatne revizije, odobravaju ih svi eksperti uključeni u Radnu grupu. CPG je odobrio objavljivanje finalnog dokumenta u časopisu European Heart. Zadatak razvoja Vodiča pokriva ne samo integraciju najnovijih istraživanja već i stvaranje edukativnih sredstava i sprovođenje programa preporuka. Da bi se primenile smernice, proizvedene su i džepne verzije vodiča, zbirke slajdova, knjižice sa osnovnim porukama i elektronska verzija za digitalne aplikacije (smartfonove, itd.). Ove verzije su skraćene, a ukoliko je potrebno, uvek može da se pogleda proširena verzija koja je besplatna I dostupna na vebsajtu. Nacionalna uduženja ESC se podstiču da prihvate, prevedu i sprovedu ESC preporuke. Implementacije programa su potrebne jer je pokazano da temeljna primena kliničkih preporuka doprinosi pozitivnom ishodu bolesti. Istraživanja i registri su potrebni da bi se proverilo da li je u svakodnevnom životu praksa u skladu sa preporukama u vodičima, što zatvara krug između kliničkog istraživanja, pisanja Vodiča, i njihove implementacije u kliničkoj praksi. Vodiči ne prevazilaze individualnu odgovornost zdravstvenih radnika da donesu adekvatnu odluku u slučaju pojedinačnog pacijenta, u dogovoru sa tim pacijentom, a kada je adekvatno i potrebno I sa pacijentovim starateljem. Odgovornost zdravstvenog radnika je I u tome što treba da proveri pravila i propise o primeni lekova i uređaja u vreme njihovog propisivanja.

Tabela 1. Klase preporuka

Klase preporuka	Definicija
Klasa I	Dokazi i/ili opšta saglasnost da je je dato lečenje ili procedura korisna i efikasna.
Klasa II	Protivurečni dokazi i/ili razlike u mišljenju o korisnosti/efikasnosti datog lečenja ili procedure
Klasa IIa	Procena dokaza/mišljenja je u prilog korisnosti/efikasnosti
Klasa IIb	Korisnost/efikasnost nije dovoljno dobro odredjena dokazima/mišljenjem
Klasa III	Dokaz ili opšta saglasnost da lečenje/procedura nije korisna, a u nekim slučajevima može biti i štetna.

Tabela 2. Nivoi dokaza

Nivo dokaza A	Podaci izvedeni iz više randomizovanih kliničkih studija ili meta-analiza
Nivo dokaza B	Podaci izvedeni iz jedne randomizovane kliničke studije ili velikih ne-randomizovanih studija
Nivo dokaza C	Saglasnost mišljenja stručnjaka i/ili male studije, retrospektivne studije, registri

Uvod

2.1 Zašto su nam potrebne nove preporuke o valvularnim bolestima srca?

Mada su valvularne bolesti srca (VHD) manje zastupljene u industrijalizovanim zemljama nego koronarna arterijska bolest (CAD), srčana insuficijencija (SI) i hipertenzija (HTA) preporuke su potrebne i u ovoj oblasti zbog toga što je valvularna bolest česta i zahteva intervenciju.[1,2] Odlučivanje za intervenciju je složeno, jer se često VHD otkrije u starijem dobu i, kao posledica toga, postoji veća učestalost komorbiditeta, što doprinosi povećanom riziku od intervencije.[1,2] Još jedan važan aspekt savremenog VHD je sve veći broj prethodno operisanih pacijenata koji se javljaju sa daljim problemima[1]. Nasuprot tome, reumatska valvularna bolest ostaje veliki problem javnog zdravlja u zemljama u razvoju, gde pretežno pogađa mlade osobe[3].

U poređenju sa drugim srčanim bolestima, postoji malo istraživanja u oblasti VHD i randomizovana klinička istraživanja su naročito retka.

Konačno, podaci iz Ankete o Euro Heart VHD,[4,5] potvrđeni drugim kliničkim studijama, pokazuju da postoji realna razlika između postojećih smernica i njihove efikasne primene.[6-9]

Mi smo smatrali da je ažuriranje postojećih ESC preporuka,[8] objavljenih 2007. godine potrebno iz nekoliko razloga.

- Prvo, novi dokazi su sakupljeni, posebno o stratifikaciji rizika, pored toga, dijagnostičke metode, posebno ehokardiografija i terapijske opcije su se promenile usled daljeg razvoja hirurške zamene zalistka i uvođenja perkutane interventnih tehnika, uglavnom transkateterske implantacije aortnog zalistka (TAVI) i perkutane popravke zalistka „edge to edge".Ove promene su uglavnom vezane za pacijenate sa aortnom stenozom (AS) i mitralnom regurgitacijom (MR).
- Drugo, značaj zajedničkog pritupa kardiologa i kardiohirurga u tretmanu bolesnika sa VHD-posebno kada su pod povećanim perioperativnim rizikom, doveo je do stvaranja zajedničkog dokumenta od ESP i EACTS. Očekuje se da će ovaj zajednički napor obezbediti sveobuhvatniji pogled i nakon toga olakšati sprovođenje ovih smernica u obe zajednice.

2.1 Sadržaj ovih preporuka

Ove preporuke se fokusiraju na stečene VHD, usmerene su na tretman i ne bave se endokarditisom i urođenim valvularnim bolestima, uključujući bolest plućnog zalistka pošto su nedavno objavljene preporuke ESC koje se bave tim temama.[10,11] Konačno, ovim preporukama nije namera da uključe detaljne informacije koje su sadržane u preporukama ESC iz drugih oblasti, stavova i ekspertskih konsenzus članaka kao i specifičnih poglavlja ESC udžbenika kardiovaskularne medicine. [12]

2.2 Kako koristiti ove preporuke

Komitet naglašava da mnogi faktori konačno određuju najprikladnije lečenje svakog pojedinačnog pacijenta u okviru date zajednice. Ovi faktori uključuju dostupnost dijagnostičke opreme, ekspertizu kardiologa i hirurga, posebno u oblasti zamene zalistka i perkutanih intervencija i, pre svega, želje dobro informisanih bolesnika. Osim toga, zbog nedostatka dokaza zasnovanih na podacima u oblasti VHD, većina preporuka je u velikoj meri rezultat stručnog konsenzusa mišljenja. Dakle, odstupanje od ovih smernica može biti prikladno u određenim kliničkim uslovima.

3. Opšti komentari

Ciljevi procene bolesnika sa VHD su da dijagnostikuje, kvantifikuje i proceni mehanizam VHD, kao i njegove posledice. Konzistentnost između rezultata dijagnostičkih ispitivanja i kliničkih nalaza treba proveriti na svakom koraku procesa donošenja odluka. Odlučivanje treba da bude od strane „kardiohirurškog tima" sa posebnim iskustvom u VHD, koji sem kardiologa, i kardiohirurga, uključuje radiologa, anesteziologa i, ako je potrebno, lekara opšte prakse, specijalistu gerijatrije ili specijalistu intenzivne nege. Ovaj timski pristup je posebno preporučljiv kod bolesnika sa visokim rizikom, a značajan je i za druge podgrupe, kao što su asimptomatski bolesnici, gde je procena mogućnosti rekonstrukcije zalistka ključna komponenta u donošenju odluka.

Odlučivanje se može sažeti u skladu sa pristupom opisanim u tabeli 3. Konačno, indikacije za intervenciju i koji tip intervencije treba izabrati, uglavnom se baziraju na komparativnoj proceni spontane prognoze i rezultata intervencije, prema karakteristikama VHD i komorbiditetima.

Tabela 3. Ključna pitanja u proceni bolesnika za intervenciju na zalistku

- Da li je bolest zalistka značajna?
- Da li bolesnik ima simptome?
- Da li su simptomi vezani za bolest zalistka?
- Koje je očekivano trajanje životaa i kvalitet života?
- Da li očekivana korist od intervencije (vs spontani ishod) nadmašuje rizik?
- Koje su želje bolesnika?
- Da li se raspolaže sredstvima potrebnim za intervenciju?

[a]Očekivano trajanje života treba proceniti na osnovu starosti, pola, komorbiditetima i proseku za određenu zemlju.

3.1 Procena bolesnika

3.1.1 Klinička procena

Uvid u stanje bolesnika se dobija procenom simptoma i udruženih komorbiditeta. Bolesnik se ispituje o načinu života da bi se otkrile progresivne promene u dnevnim aktivnostima i da bi se izbegla subjektivnost u prikazivanju simptoma, posebno kod starijih. Kod hroničnih stanja postoji adaptacija na simptome što takođe treba uzeti u obzir. Razvijanje simptoma je česta indikacija za intervenciju. Bolesnike koji trenutno poriču simptome , ali se leče od srčane insuficijencije treba smatrati simptomatskim. U prisustvu komorbiditeta značajno je proceniti uzrok simptoma.

Ispitivanje bolesnika je takođe važno u proceni kvaliteta praćenja, kao i efektivnosti profilakse endokarditisa i kada je potrebno reumatske groznice. Kod bolesnika na hroničnoj antikoagulantnoj terapiji potrebno je proceniti redovnost korišćenja terapije kao i tražiti dokaze tromboembolizma i krvarenja.

Klinički pregled igra značajnu ulogu u otkrivanju asimptomatskih bolesnika sa VHD. On predstavlja prvi korak u konačnoj dijagnozi VHD i proceni njene značajnosti imajući u vidu da šum male jačine može postojati kod značajne VHD naročito kada je prisutna srčana slabost. Kod bolesnika sa veštačkim zaliscima treba biti svestan svake promene šuma ili zvuka veštačkog zalistka.

Elektrokardiogram (EKG) i rendgenski snimak grudnog koša se često rade u okviru kliničkog pregleda. Osim uvećanja srca, analiza plućne vaskulature na rendgenskom snimku grudnog koša je ključna u proceni dispnee ili kliničkih znakova srčanog popuštanja.[13]

Tabela 4. Ehokardiografski kriterijumi za definisanje značajne valvularne stenoze

	Aortna stenoza	Mitralna stenoza	Trikusipdna stenoza
Površina ušća (cm2)	<1.0	<1.0	-
Indeksirana površina ušća (cm2/m2 BSA)	<0.6	-	-
Srednji gradijent (mmHg)	>40a	>10b	≥5
Maksimalna brzina protoka (m/s)	>4.0a	-	-
Odnos brzine	<0.25	-	-

BSA – telesna površina, [a]Kod bolesnika sa normalnim udarnim volumenom/transvalvularnim protokom, [b]Korisno kod bolesnika u sinusnom ritmu/da se interpretira prema srčanoj frekvenci, Usvojeno iz Baumgartner et al[15]

3.1.2 Ehokardiografija

Ehokardiografija je ključna tehnika koja se koristi za potvrdu dijagnoze VHD, kao i njene značajnosti i prognoze. Treba da je izvodi i interpretira dobro obučen lekar.[14] Indikovana je kod svakog bolesnika sa šumom osim ako ne postoji sumnja na oboljenje srčanih zalistaka nakon kliničkog pregleda.

Procena značajnosti stenotične bolesti srčanih zalistaka treba da sadrži procenu površine zalistka sa merama koje su zavisne od protoka kao što su srednji gradijent pritiska i maksimalna brzina protoka (tabela 4). Mere zavisne od protoka daju dodatne informacije i imaju prognostički značaj.

Procena valvularne regurgitacije treba da kombinuje različite mere uključujući kvantitativne mere kao što su „vena contracta" i efektivna veličina regurgitirajućeg otvora (EROA) koje su manje zavisne od stanja protoka nego veličina mlaza kolor doplera (tabela 5).[16,17] Ipak sve kvantitativne procene imaju ograničenja. Konkretno, one kombinuju brojna merenja, vrlo su osetljive na greške u merenjima i veoma su zavisne od operatera; tako da njihovo korišćenje zahteva iskustvo i integraciju brojnih parametara pre nego oslanjanje na jedan parameter.

Tako da, kada se procenjuje značajnost VHD, potrebno je proveriti slaganje različitih ehokardiografskih merenja, kao i anatomiju i mehanizam VHD. Takođe je potrebno proveriti njihovo slaganje sa kliničkom procenom.

Ehokardiografija treba da uključi procenu svih zalistaka, tražeći eventualno povezane bolesti ostalih zalistaka i aorte.

Pokazatelji uvećanja i funkcije leve komore su značajni prognostički faktori. Mada dijametri daju manje značajne informacije o veličini leve komore nego volumeni, njihov prognostički značaj je više ispitivan. Dimenzije leve komore treba indeksirati na telesnu površinu (BSA). Korišćenje indeksiranih vrednosti je posebno potrebno kod niskih i mršavih ljudi, a treba ga izbegavati kod ljudi koji su ekstremno gojazni. (BMI>40 kg/m^2).

Mere izvedene iz tkivnog doplera i strejna mogu biti od koristi u otkrivanju ranog oštećenja funkcije LV, ali nedostaju podaci koliko su oni prognostički značajni.

Konačno treba proceniti plućni pritisak kao i funkciju desne komore[18]. Trodmenzionalna ehokardiografija (3DE) je korisna u proceni anatomskih specifičnosti koje mogu uticati na odluku o tipu planirane intervencije (naročito kod mitralnog zalistka).[19]

Transezofagusnu ehokardiografiju (TEE) treba koristiti kada se transtoraksnom ehokardiografijom (TTE) ne može dobiti kvalitan prikaz ili kada se sumnja na trombozu, disfunkciju proteze ili endokarditis. Intraproceduralna TEE omogućava praćanja rezultata hirurške intervencije ili perkutanih procedura. Intraoperativni TEE visokog kvaliteta je obavezan kod rekonstrukcije zalistka. Trodimenzijski TEE je detaljniji pregled anatomije zalistka nego dvodimenzijski.

3.1.3 Druga neinvazivna ispitivanja

3.1.3.1 Stres test

Stres test se koristi za procenu valvularne mane i njenih posledica, ali ne i za dijagnozu pridružene koronarne bolesti (CAD). Funkcionalni testovi koji se koriste u dijagnozi CAD nemaju dobru prediktivnu vrednost kod postojanja VHD i ne koriste se u tim situacijama.[20]

EKG u naporu

Osnovna svrha testa opterećenjem je da objektivizira pojavu simptoma kod bolesnika koji tvrdi da ih nema ili nije siguran. Test opterećenjem ima dodatnu vrednost u stratifikaciji rizika kod bolesnika sa AS.[21] Testom opterećenja se takođe utvrđuje nivo dozvoljene fizičke aktivnosti, uljučujući i bavljenje sportovima.

Ehokardiografija u naporu

Stres ehokardiografijom se može utvrditi eventualno srčano porekli dispnee koja je nespecifičan simptom – dokazujući, na primer porast mitralne regurgitacije/gradijenta nad aortom i sistolnog plućnog pritiska. Ima dijagnostički značaj kod prolazne ishemijske MR koja se može prevideti kod pregleda u stanju mirovanja. Prognostički značaj stres eho testa je dokazan kod MR i AS. Ipak, ova tehnika nije široko dostupna, može biti tehnički zahtevna i zahteva specifičnu stručnost.

Drugi testovi opterećenjem

Ispitivanje rezerve protoka (takođe nazvane kontarktilna rezerva) koristeći niskodozni dobutaminski stres test je korisno kod procene značajnosti i operativne stratifikacije rizika kod AS sa oštećenom funkcijom LV i niskim gradijentom[22].

3.1.3.2 Srčana magnetna rezonanca

Kod bolesnika sa lošim ehokardiografskim prikazom ili diskrepantnim rezultatima srčana magnetna rezonanca (CMR) se koristi za procenu značajnosti valvularnih lezija (naročito regurgitirajućih) i za procenu komorskih volumena i sistolne funkcije. Reproducibilnost merenja kod CMR je daleko veća nego kod ehokardiografije[23].

Tabela 5. Ehokardiografski kriterijumi za definisanje značajne valvularne regurgitacije

	Aortna regurgitacija	Mitralna regurgitacija		Trikuspidna regurgitacija
Kvalitativno				
Morfologija zalistka	Nenormalan/prolaps/ veliki defekt koaptacije	Prolaps zalistka/rupture papilarnog mišića, veliki defekt koaptacije		Nenormalan/prolaps/ veliki defekt koaptacije
Regurgitirajući mlaz (kolor dopler)	Veliki kod centralnih mlazeva, varijabilan kod ekscentričnih mlazeva	Vrlo veliki centralni mlaz ili ekscentričan mlaz koji vrtloži		Vrlo veliki centralni mlaz ili ekscentrični mlaz koji udara u zida
CW signal regurgitirajućeg mlaza	Gust	Gust/trouglast		Gust/trouglast)u masivnoj regurgitaciji brzo dostiže vrh (<2m/s)
Drugo	Holodijastolna reverzija protoka u nishodnoj aorti (EDV >20cm/s)	Velika zona konvergencije protoka		-
Semikvantitativno				
Vena kontakta širina (mm)	>6	≥7 (>8 za biplane)b		≥7a
Uzvodni venski tokc	-	Reverzan sistolni protok u plućnim venama		Reverzan sistolni protok u hepatičnim venama
Utok	-	E talas dominantan≥1.5m/sd		E talas dominantan≥1m/se
Drugo	Poluvreme pada pritiska<200ms	TVI mitralno/TVI aortni >1.4		PISA radijus >9mmg
Kvantitativni		Primarna	Sekundarnah	
EROA (mm2)	≥30	≥40	≥20	≥40
R Vol (ml/udar)	≥60	≥60	≥30	≥45
+ uvećanje srčanih šuplji-na/sudova	LV	LV, LA		RV,RA, donja šuplja vena

CW – continuous wave (kontinuirani dopler); EDV – end-diastolic velocity (enddijastolna brzina); EROA – effective regurgitant orifice area (efektivna veličina regurgitirajućeg otvora); LA – left atrium (leva pretkomora); LV – left ventricle (leva komora); PISA – proxymal isovelocity surface area (površina proksimalne izobrzinske krive); RA – right atrium (desna pretkomora); RV – right ventricle (desna komora); R Vol – volumen regurgitacije; TR – trikuspidna regurgitacija; TVI – time velocity integral (integral brzina vreme)
[a]Na Nikvistovom limitu 50–60cm/s, [b]Prosek apikalnog četvorošupljinskog i dvošupljnskog prikaza, [c]Osim ako postoji razlog za sistolno zatupljivanje (fibrilacija pretkomora, povećan pritisak u pretkomorama), [d]U odsustvu drugih razloga povećanog pritiska u levoj pretkomori i mitralne stenoze, [e]U odsustvu drugih razloga povećanog protoka u desnoj pretkomori, [f]poluvreme pada pritiska se skraćuje sa povećanjem dijastolnog pritiska u levoj komori, terapijom vatzodilatatorima i kod bolesnika da dilatiranom rastegljivom aortom ili izduženom kod hronične aortne regurgitacije, [g]Bazalno prebacivanje Nikvistovog limita 28cm/s, [h]Različite granične vrednosti se koriste kod sekundarne MR gde je EROA>20mm^2 i regurgitirajući volumen >30ml da bi se otkrili bolesnici sa povećanim rizikom od srčanih događaja. Usvojeno od Lancellotti et al.[16,17]

CMR je referentna metoda za procenu volumena i funkcije desne komore tako da je korisna za procenu posledica trikuspidne regurgitacije (TR). U praksi rutinska upotreba CMR je ograničena u odnosu na ehokardiografiju zbog manje raspoloživosti.

3.1.3.3 Kompjuterizovana tomografija

Multi slajs kompluterizovana tomografija (MSCT) doprinosi proceni značajnosti valvularne bolesti, naročito kod AS, indirektno određivanjem obima kalcifikacija ili direktno planimetrijskim merenjem zalistka[24,25]. Najviše se koristi za procenu značajnosti i lokalizacije aneurizme ascedentne aorte. Zahvaljujući negativnom prediktivnom značaju MSCT može biti koristan u isključivanju CAD kod bolesnika koji imaju nizak rizik za aterosklerozu.[25] MSCT ima značajnu ulogu u pripremi bolesnika visokog rizika sa AS kod kojih se planira TAVI.[26,27.] Treba uzeti u obzir i rizik od izlaganja zračenju, kao i rizik od bubrežne insuficijencije usled injekcije kontrasta.

CMR kao i MSCT zahtevaju uključenje radiologa/kardiologa sa stručnošću u oblasti VHD.

3.1.3.4 Fluoroskopija

Fluoroskopija je specifičnija od ehokardiografije u proceni valvularnih ili anularnih kalcifikacija. Takođe je korisna u proceni kinetike okludera mehaničkih proteza.

3.1.3.5 Radionuklidna angiografija

Radionuklidna angiografija pruža pouzdanu i reproducibilnu procenu ejekcione frakcije LV kod bolesnika u sinusnom ritmu. Može se koristiti kada procena EF ima najznačajniju ulogu u donošenju terapijske odluke, naročito kod asimptomatskih bolesnika sa valvularnim regurgitacijama.

3.1.3.6 Biomarkeri

Nivo B-tip natriuretskog peptida (BNP) je povezan sa funkcionalnom klasom i prognozom, naročito kod AS i MR[29]. Za sada su ograničeni dokazi koji se tiču njihovog rastućeg značaja u stratifikaciji rizika.

3.1.4 Invazivna ispitivanja

Koronarna angiografija

Koronarna angiografija se široko koristi za detekciju pridružene koronarne bolesti kod pripreme za hirurgiju (tebela 6).[20] Poznavanje koronarne anatomije doprinosi stratifikaciji rizika i procenjuje da li je potrebna konkomitantna koronarna revaskularizacija.

Koronarna angiografija se može izostaviti kod mladog bolesnika bez faktora rizika za aterosklerozu (muškarci ispod 40 g i premenopauzalne žene) i u retkim prilikama kada rizik premašuje korist , npr. akutna disekcija

Tabela 6. Lečenje koronarne bolesti kod bolesnika sa bolešću zalistka

	Klasa[a]	Nivo[b]
Dijagnoza koronarne bolesti		
Koronarografija se preporučuje kod bolesnika sa značajnom bolešću zalistka i sledećim: - anamneza koronarne bolesti, - sumnjiva ishemija miokarda,[d] - sistolna disfunkcija leve komore, - kod muškaraca preko 40 g i žena u menopauzi, - ≥1 kardiovaskularnim faktorom rizika.	I	C
Koronarna angiografija je potrebna u evaluaciji sekundarne mitralne regurgitacije	I	C
Indikacije za revaskularizaciju miokarda		
CABG je indikovan kod bolesnika za primarnu operaciju aortnog/mitralnog zalistka i stenozu koronarne arterije ≥70%e	I	C
CABG treba razmotriti kod bolesnika za primarnu operaciju aortnog/mitralnog zalistka i stenozu koronarne arterije 50–70 %.	IIa	C

CABG – aorto-koronarni bajpas, [a]Klasa preporuka, [b]Nivo dokaza, [c]Multi slajs kompjuterizovana tomografija se može koristiti da se isključi koronarna bolest kod bolesnika koji su u niskom riziku od ateroskleroze, [d]Bol u grudima, patološki rezultat neinvazivnog testa, [e]≥50% za stenozu glavnog stable, Preuzeto iz Wijns et al.[20]

aorte, velika vegetacija na aorti ispred ušća koronarnih krvnih sudova ili okluzovna tromboza veštačke proteze koja vodi hemodinamskoj nestabilnosti.

Srčana kateterizacija

Merenje pritiska i udarnog volumena ili izvođenje komorske angiografije ili aortografije je rezervisano za situacije kada je neinvazivna procena neinformativna ili se ne slaže sa kliničkim nalazima. Obzirom na potencijalne rizike srčanu kateterizaciju ne treba izvoditi rutinski sa koronarnom angiografijom.

3.1.5 Procena komorbiditeta

Kliničkom procenom se vrši izbor specifičnih pregleda da bi se procenili komorbiditeti. Komorbiditeti koji se najčešće javljaju su periferna ateroskleroza, disfunkcija bubrega ili jetre, i hronična obstruktivna bolest pluća. Specifični skorovi omogućavaju procenu mentalnih i funkcionalnih kapaciteta što ima važan prognostički značaj, posebno kod starijih. Stručno mišljenje specijaliste gerijatrije je naročito značajno u ovim situacijama.

3.2 Profilaksa endokarditisa

Indikacije za antibiotsku profilaksu su značajno sužene u skorašnjim ESC preporukama[10]. Antibiotsku profilaksu treba razmatrati u visokorizičnim procedurama kod visokorizičnih bolesnika, kao što su bolesnici sa veštačkim zaliscima ili bolesnici kod kojih je korišćen veštački materijal kod rekonstrukcije zalistaka ili bolesnici koji su preboleli endokarditis ili imaju urođeno srčano oboljenje prema važećim ESC preporukama. Ipak prevencija infektivnog endokarditisa ostaje značajna kod bolesnika sa VHD, što uključuje dobru oralnu higijenu i aseptičke mere tokom kateterizacije ili bilo koje invazivne procedure kako bi se smanjila stopa jatrogenog infektivnog endokarditisa.

3.3 Profilaksa reumatske groznice

Kod bolesnika sa reumatskom bolesti srca preporučuje se dugotrajna profilaksa reumatske groznice. Koristi se penicillin bar 10 godina od poslednje epizode akutne reumatske groznice, ili do 40 godina starosti. Doživotnu profilaksu treba razmotriti kod visokorizičnih bolesnika sudeći prema značajnosti VHD i izloženosti grupi A Streptokoka.[30]

3.4 Stratifikacija rizika

Mnogi registri širom sveta konstantno pokazuju da se u sadašnjoj praksi malo koriste terapijske intervencije kod visokorizičnih simptomatskih bolesnika sa VHD iz razloga koji često nisu opravdani. To ukazuje na potrebu pažljive stratifikacije rizika.[31]

U odsustvu dokaza randomizovanih kliničkih studija, odluka da se interveniše kod bolesnika sa VHD se zasniva na individualnoj analizi rizik-korist što sugoriše da poboljšanje prognoze u poređenju sa prirodnim tokom bolesti nadmašuje rizik intervencije (tabela 7) i potencijalne kasne posledice, naročito komplikacije vezane za protezu.[32–35]

Operativni mortalitet se može proceniti raznim skorovima koristeći kombinaciju faktora rizika.[36] Dva najčešće korišćena skora su Euro SCORE (European System for Cardiac Operative Risk Evaluation; www.euroscore.org/calc.html) i STS (Society of Thoracic Surgeons) score (http://209.220.160.181/STSWebRiskCalc261/) od kojih poslednji ima prednost, specifičan je za VHD, ali manje jednostavan za korišćenje od EuroSCORA. Postoje i drugi scoring sistemi specifično dizajnirani za VHD.[37,38] Različiti skorovi obezbeđuju relativno dobru diskriminaciju (razlikovanje između visoko i niskorizičnih bolesnika), ali im nedostaje tačnost u proceni operativnog mortaliteta individualnih bolesnika zbog nedovoljno dobre kalibracije (razlike između očekivanog i zapaženog rizika).[39] Kalibracija je loša kod visokorizičnih bolesnika, sa precenjivanjem operativnog rizika, posebno kod Logističkog EuroSCORE.[40,41] To ističe značaj sveobuhvatnijeg pristupa kod procene rizika i tipa intervencije za određenog bolesnika. Prediktivna vrednost skorova rizika se može poboljšati sledećim merama ponavljana rekalibracija skorova tokom vremena, kao što je slučaj sa STS i EuroSCORE sa EuroSCORE II – dodavanje varijabli, posebno pokazatelja mentalnih i funkcionalnih kapaciteta i slabosti kod starijih – dizajniranje odvojenih skorova rizika za određene

Tabela 7. Operativni mortalitet nakon operacije bolesti zalistka

	EACTS (2010)	STS (2010)	UK (2004-2008)	Nemačka (2009)
Zamena aortnog zalistka, bez CABG (%)	2.9 (40 662)	3.7 (25 515)	2.8 (17 636)	2.9 (11 981)
Zamena aortnog zalistka, + CABG (%)	5.5 (24 890)	4.5 (18 227)	5.3 (12 491)	6.1 (9 113)
Rekonstrukcija mitralnog zalistka, bez CABG (%)	2.1 (3 231)	1.6 (7 293)	2 (3 283)	2 (3 3359
Zamena mitralnog zalistka, bez CABG (%)	4.3 (6 838)	6.0 (5 448)	6.1 (3 614)	7.8 (1 855)
Rekonstrukcija/zamena mitralnog zalistka + CABG (%)	6.8/11.4 (2515/1612)	4.6/11.1 (4741/24724)	8.3/11.1 (2021/1337)	6.5/14.5 (1785/837)

( ) – broj bolesnika; CABG – aorto-koronarni bajpas; EACTS – Evropska asocijacija za kardiotorakalnu hirurgiju;[32] STS – Society of thoracic surgeons (Udruženje torakalnih hirurga) (USA); Mortalitet kod STS uključuje prve i reintervencije;[33] UK=Ujedinjeno kraljevstvo;[34] Nemačka[35]

subgrupe, kao što su stariji bolesnici kod kojih se planira kombinovana valvularna i koronarna hirurgija.[42]

Slično, treba razviti specifične scoring sisteme za predviđenje ishoda nakon transkateterskih intervencija na zaliscima.

Prirodni ishod VHD treba predvideti iz savremenih serija, ali ne postoje specifični scoring sistemi na tu temu. Određeni scoring sistemi omogućavaju procenu očekivanog trajanja života sudeći prema godinama starosti, komorbiditetima, i pokazateljima mentalnih i funkcionalnih kapaciteta. Treba uzeti u obzir i očekivani kvalitet života.

Treba razmotriti lokalne resurse, naročito mogućnost rekonstrukcije zalistka kao i iskustva u hirurgiji i perkutanim intervencijama specifičnog centra.[44]

Za kompleksnije procedure, kao što je složena rekonstrukcija zalistka, treba bolesnike uputiti u specijalizovani centar sa iskustvom.[45] Konačno, odluku koji je tretman optimalan treba doneti zajednički, multidisciplinarni kardiohiruški tima u dogovoru sa samim bolesnikom i njegovom familijom nakon što su dobro informisani.[46]

3.5 Tretman pridruženih stanja

3.5.1 Koronarna bolest

Ne preporučuje se korišćenje testa opterećenja za otkrivanje CAD kod bolesnika sa značajnom VHD zbog malog dijagnostičkog značaja i potencijalnih rizika.

Postupak kod pridružene CAD je prikazan u tabeli 6 i detaljno opisan sa specifičnim preporukama.[20]

3.5.2 Aritmije

Kod bolesnika sa VHD i bilo kojim tipom atrijalne fibrilacije preporučuje se oralna antikoagulantna Th sa INR-om između 2 i 3 uzimajući u obzir i rizik od krvarenja.[47] Kod bolesnika sa veštačkim zaliscima može biti potreban veći nivo antikoaguacije (vidi sekciju 11). Ne preporučuje se zamena antagonista vitamina K novim lekovima, zato što ne postoje specifične studije kod bolesnika sa VHD. Ne preporučuje se kardioverzija pre intervencije kod bolesnika sa VHD jer ne obezbeđuje trajan sinusni ritam, sem kada AF uzrokuje hemodinamsku nestabilnost. Kardioverziju treba pokušati nakon intervencije, osim u slučajevima dugotrajne hronične AF.

Kod bolesnika kod kojih se planira hirurgija zalistka treba razmotriti hirušku ablaciju kod simptomatskih bolesnika sa AF, kao i kod asimtomatskih, ako je izvodljiva uz minimalan rizik.[47] Odluku treba doneti u zavisnosti od kliničkih varijabli kao što su godine starosti, trajanje AF i veličina leve pretkomore.

Nema dokaza da treba vršiti rutinsko zatvaranje aurikule leve pretkomore, osim kada je u sklopu hirurške ablacije AF.

4. Aortna regurgitacija

Uzrok aortne regurgitacije može biti primarno poremećaj aortnih listića i/ili geometrije aortnog korena. U zapadnim zemljama kod bolesnika operisanih zbog izolovane AR uglavnom je prisutno ovo poslednje. Kongenitalne anomalije, uglavnom bikuspidna valvula, su sledeći najčešći nalaz.[1,12,48] Analiza uzroka AR utiče na odluku o načinu lečenja posebno kada se razmatra rekonstrukcija zalistka.

4.1 Procena

Inicijalni pregled treba da uključi detaljnu kliničku procenu. AR se dijagnostikuje nalazom dijastolnog šuma odgovarajućih karakteristika. Pojačane arterijske pulsacije i nizak dijastolni pritisak predstavljaju prve i najvažnije kliničke znake za kvantifikaciju AR. Kod akutne AR perifereni znaci su ublaženi što je u suprotnosti sa lošim kliničkim stanjem.[12]

Osnovne smernice za korišćenje neinvazivne i invazivne dijagnostike date su u preporukama koje su navedene u *Opštim komentarima* (sekcija 3).

Specifičnosti vezane za AR:

- Ehokardiografija je ključno sredstvo u dijagnostici i kvantifikaciji AR, koristeći kolor dopler (posebno vena contracta) i pulsni dopler (dijastolna reverzija protoka u nishodnoj aorti).[16,49] Kvantitativna dopler ehokardiografija (PISA), manje je osetljiva na uslove punjenja, ali je manje jasno definisana nego kod MR i u ovom trenutku se ne koristi rutinski.[50] Kriterijumi za definisanje značajne AR su opisani u tabeli 5.
  Ehokardiografija je takođe značajna u opisivanju mehanizma AR, opisivanju anatomije zalistka i izvodljivosti rekonstrukcije zalistka.[16,49] Ascedentnu aortu treba meriti na 4 nivoa: anulus, sinusi Valsalve, sinotubular-

ni spoj, i ascedentna Ao.[51] Indeksiranje dijametara aorte prema BSA treba vršiti za niske bolesnike, male telesne mase. Aneurizma/dilatacija ascedentne aorte, posebno na sinotubularnom nivou, može da uzrokuje sekundarnu AR.[52] Ako se planira rekonstrukcija aortnog zalistka ili operacija u kojoj se ne interveniše na samom zalistku preoperativno se može obaviti TEE pregled radi uvida u anatomiju aortnog zalistka i ascedentne aorte. Kod rekontrukcije aortnog zalistka obavezan je intraoperativni TEE radi procene funkcionalnih rezultata i identifikacije bolesnika koji su u riziku za ranu ponovnu pojavu AR.[53]

Ključno je utvrđivanje funkcije i dimenzija LV. Preporučljivo je indeksiranje prema BSA naročito za bolesnike sa malom masom (BSA<1,68 m²).[54] Novi parametri dobijeni pomoću 3DE, tkivnim doplerom i strejnom mogu naći svoje mesto u budućnosti.[55]

- CMR ili MSCT se preporučuju za procenu aorte kod bolesnika sa Marfanovim sindromom, ili ako je uvećana aorta viđena na ehokardiografskom pregledu naročito kod bolesnika da bikuspidnom aortnom valvulom.

4.2 Prirodni tok

Bolesnici sa akutnom značajnom aortnom regurgitacijom do koje je došlo usled disekcije aorte ili infektivnog endokarditisa imaju lošu prognozu bez intervencije usled hemodinamske nestabilnosti.

Bolesnici sa simptomatskom hroničnom značajnom AR imaju takođe lošu prognozu. Od pojave simptoma mortalitet kod bolesnika koji nisu lečeni hirurški raste 10–20% godišnje.[57]

Prognoza je dobra kod asimptomatskih bolesnika sa značajnom hroničnom AR i normalnom funkcijom LV. Ipak, kod kod porasta endsistolnog dijametra LV >50mm (LVESD) raste verovatnoća za smrtni ishod, simptome ili disfunkciju LV na 19% godišnje.[57-59]

Prirodan tok aneurizme ascedentne aorte i korena aorte najbolje je opisan kod Marfanovog sindroma.[60] Najsnažniji prediktori smrtnog ishoda i aortnih komplikacija su dijametar korena i pozitivna porodična anamneza za akutne kardiovaskularne događaje (aortna disekcija, iznenadna srčana smrt).[61] Pretpostavka je da druge sistemske sindrome koji su povezani sa dilatacijom ascedentne aorte treba posmatrati kao Marfanov sindrom i podrazumevati sličnu prognozu. Bolesnici sa bikuspidnom aortnom valvulom su ranije smatrani za grupu sa povećanim rizikom za disekciju. Skorašnji dokazi ukazuju da je to najverovatnije usled povećane prevalence dilatacije ascedentne aorte.[62] Ipak, uprkos bržem porastu doijametra aorte, nije jasno da li je povećana učestalost aortnih komplikacija, u poređenju sa bolesnicima sa trikuspidnom aortnom valvulom i istim dijametrom aorte.[63,64]

4.3 Rezultati hirurgije

Tradicionalno lečenje izolovane aortne regurgitacije je značilo zamenu aortnog zalistka. U poslednjih 20 godina razvile su se strategije za rekonstrukciju aortnog zalistka kod trivelarnih zalistaka i kongenitalnih anomalija.[65–67] Kada postoji aneurizma aortnog korena kovencionalna hirurška tehnika je podrazumevala zamenu aorte i zalistka sa reimplantacijom koronarnih arterija. U centrima sa iskustvom, posebno kod mlađih bolesnika kod kojih postoji kombinovana dilatacija aortnog korena i regurgitacija primenjuje se zamena aorte bez zamene zalistka.[65-67]

Kod normalog dijametra aortnog korena može se učiniti suprakoronarna zamena ushodne aorte sa rekonstrukcijom zalistka ili bez nje.[67]

Zamena aortnog zalistka plućnim autograftom retko se koristi i to uglavnom kod mladih bolesnika (<30 god.).

Najrasprostranjenija tehnika trenutno je zamena zalistka, mada u iskusnim centrima raste procenat rekonstrukcija. Kalcifikacije i retrakcija listića su najčešće neželjene posledice rekonstrukcija. Kada je u pitanju izolovana operacija aortnog zalistka, bilo da je zamena ili rekontrukcija operativni mortalitet je nizak (1–4%)[32–35,66]. Mortalitet raste sa starošću, oštećenom funkciom LV, i udruženom hirurškom revaskularizacijom gde raste na 3-7%[32–35]. Najznačajniji prediktori operativnog mortaliteta su starije doba, veća preoperativna funkcionalna klasa, LVEF<50 %, i LVESD>50 mm. Hirurgija aortnog korena sa reimplantacijom koronarnih arterija ima nešto veći mortalitet nego izolovana hirurgija aortnog zalistka. U centrima sa iskustvom, kombinovan tretman aneurizme ascedentne aorte sa ili bez zamene zalistka, kod mladih osoba se vrši sa veoma malom smrtnošću.[66,67]

Mortalitet raste sa hitnošću procedure kod disekcije aorte. Kod bioloških kao i mehaničkih zalistaka postoji dugoročni rizik od komplikacija (vidi sekciju 11).

4.4 Indikacije za hirurgiju

Kod akutne simptomatske značajne aortne regurgitacije indikovana je hitna hirurgija.

Kod hronične značajne AR terapijski ciljevi su preveniranje smrtnog ishoda, umanjenje simptoma, preveniranje srčane insuficijencije i izbegavanje aortnih komplikacija kod bolesnika sa aneurizmom aorte.[69]

Na osnovu robusnih opservacionih dokaza date su preporuke za hirurgiju (tabela 8A, B, figura 1):

- Kod bolesnika sa značajnom AR pojava simptoma je indikacija za hirurgiju, kao i kod bolesnika za disfunkcijom LV ili značajnom dilatacijom, nakon isključenja drugih mogućih uzroka. Mada je kod ovih bolesnika postoperativni ishod gori neko kod onih koji su ranije operisani, mogu se ostvariti prihvatljivi operativni mortaliteti, umanjenje simptoma i prihvatljivo dugoročno preživljavanje.[48,70,71]
- Hirurgija je indikovana kod asimptomatskih bolesnika sa značajnom AR i oštećenom funkcijom LV (EF<50 %) i treba je razmotriti kada je enddijastolni dijametar LV (LVEDD) >70 mm ili LVESD>50 mm (ili >25mm/m2 BSA kod niskih i mršavih bolesnika), zato što je verovatnoća da dođe do ireverzibilne disfunkcije miokarda velika ako se intervencija dalje odlaže, a postoperativni trezultati su odlični ako se operiše bez odlaganja. Kod asimptomatskih bolesnika pre donošenja konačne odluke o hirurgiji, potrebno je obezbediti dobru vizuelizaciju i potvrdu dimenzija ponovljenim merenjima. Naglo pogoršanje komorskih parametara je takođe razlog za hirurgiju.

Tabela 8. Indikacije za operaciju kod (A) Značajne aortne regurgitacije (B) Bolesti aortnog korena (bez obzira na značajnost aortne regurgitacije)

	Klasa[a]	Nivo[b]	Refc
A. Indikacije za operaciju kod značajne aortne regurgitacije			
Operacija je indikovana kod simptomatskih bolesnika	I	B	59
Operacija je indikovana kod simptomatskih bolesnika sa EF u miru ≤50%	I	B	71
Operacija je indikovana kod bolesnika kod kojih se planira CABG ili operacija ushodne aorte, ili drugog zalistka	I	C	
Operaciju treba razmotriti kod simptomatskih bolesnika sa EF u miru ≤50%, sa značajnom dilatacijom LV: LVEDD>70mm, ili LV ESD>50mm ili LVESD >25mm/m2 BSA	IIa	C	
B. Indikacije za operaciju kod bolesti aortnog korena (bez obzira na značajnost aortne regurgitacije)			
Operacija je indikovana kod bolesnika koji imaju bolest aortnog korena sa maksimalnim dijametrom ushodne aortee ≥50 mm kod bolesnika sa Marfanovim sindromom	I	C	
Operaciju treba razmotriti kod bolesnika koji imaju bolest aortnog korena sa maksimalnim dijametrom ushodne aorte: ≥45 mm kod bolesnika sa Marfanovim sindromom i faktorima rizikaf ≥50 mm kod bolesnika sa bikuspidnom valvulom i faktorima rizikag ≥55 mm za druge bolesnike	IIa	C	

AR – aortna regurgitacija; BSA – telesna površina; CABG – aorto-koronarni bajpas; EF – ejekciona frakcija; LV – leva komora; LVEDD – enddijastolna dimenzija leve komore; LVESD – endsistolna dimenzija leve komore.
[a]Klasa preporuka, [b]Nivo dokaza, [c]Reference podržavaju klasu I (A+B) i IIa + IIb (A+B) preporuke, [d]Treba uzeti u obzir razlike u uzastopnim merenjima, [e]Pri odluci treba uzeti u obzir oblik različitih delova aorte. Niži prag se koristi za kombinovanu operaciju ushodne aorte kod bolesnika koji imaju indikaciju za operaciju aortnog zalistka, [f]Porodična anamneza disekcije aorte i/ili porast dijametra aorte >2 mm/godišnje (na ponavljanim merenjima koristeći istu metodu, mereći aortu na istom nivou i potvrđujući drugom tehnikom), značajna aortna ili mitralna regurgitacija, želja za trudnoćom, [g]Koarktacija aorte, sistemska hipertenzija, porodična anamneza disekcije aorte i/ili porast dijametra aorte >2 mm/godišnje, (na ponavljanim merenjima koristeći istu metodu, mereći aortu na istom nivou i potvrđujući drugom tehnikom)

- Kada postoji dilatacija ushodne aorte i aortnog korena, najbolje je definisana potreba za hirurgijom kod bolesnika sa Marfanovim sindromom. Kod graničnih slučajeva treba uzeti u obzir porodičnu anamnezu, starost bolesnika i očekivani rizik procedure. Kada postoji Marfanov sindom treba operisati kod manjeg stepena dilatacije (≥50 mm). U ranijim preporukama hirurgija je planirana kada je dijametar aorte iznosio >45 mm. Nije kod svih bolesnika nužan ovako agresivan pristup. Ipak kod postojanja faktora rizika (podatak o disekciji u porodici, porast aorte >2 mm/god. u ponovljenim merenjima i potvrđeno drugom tehnikom, značajna AR, želja za trudnoćom) treba razmotriti hirurgiju kada je dijametar aorte ≥45 mm.[61] Kada je dijametar aorte 40–45 mm i postoji podatak o rastu aorte i disekciji u porodici, ne savetuje se trudnoća.[72] Bolesnike sa manifestacijama Marfanovog sindroma, bez kompletnih kriterijuma za Marfanov sindrom treba tretirati kao bolesnike sa Marfanovim sindomom. Kod bolesnika sa bikuspidnim aortnim zalistkom i dijametrom aorte ≥50 mm odluku o operaciji treba doneti uzimajući u obzir starost bolesnika, telesnu površinu, komorbiditete, tip hirugije i prisustvo dodatnih faktora rizika (porodična anamneza, arterijska hipertenzija, koarktacija aorte, porast dijametra >2 mm/god. na ponovljenim pregledima koristeći istu tehniku ili potvrđeno drugom tehnikom). U drugim slučajevima dilatacija korena aorte ≥55 mm ukazuje da je potrebna hirurgija bez obzira na stepen AR.[73]
- Kod bolesnika kod kojih se iz drugih razloga planira operacija aortnog zalistka, udruženu zamenu aorte treba razmotriti kod dijametra >45 mm zavisno od starosti, BSA, porekla valvularne bolesti, prisustva bikuspidnog zalistka i intraoperativnog oblika i debljine ascedentne aorte.[74]
- Kada je u pitanju bolesnik niskog rizika koji je u mogućnosi da se opriše u centru sa iskustvom za operaciju, može se odlučiti i kada je dijametar aorte manji.

Za tip hirurške procedure se odlučuje na osnovu iskustva tima, prisustva aneurizme korena, karakteristika listića, očekivanog trajanja života i željenog antikoagulacionog statusa.

4.5 Medikamentna terapija

Kod bolesnika sa značajnom SI u fazi pripreme za operaciju aortnog zalistka mogu se koristiti vazodilatori i inotropni agensi. Kod bolesnika sa hroničnom značajnom AR i SI vazodilatatori (ACE inhibitori illi ARB blokatori) su korisni kada postoji hipertenzija ili je operacija kontraindikovana ili disfunkcija LV postoji i postoperativno. Pozitivan efekat ovih agenasa ili dihidropiridinskih blokatora Ca u smislu odlaganja operacije nije dokazana kod asimptomatskih bolesnika bez hipertenzije.[75]

Kod bolesnika sa Marfanovim sindromom beta-blokatori mogu usporiti dilataciju aortnog korena kao i smanjiti rizik od komplikacija i treba ih planirati pre i nakon operacije.[61]

Preliminrni dokazi ukazuju da selektivni ARB blokatori imaju povoljan efekat na aortni zid tako što čuvaju elastična vlakna. Ostaje da se u budućim istraživanjima potvrdi njihov klinički značaj.

Bolesnicima sa Marfanovim sindromom kao i ostalima koji imaju granične vrednosti dijametra aorte ne preporučuju se naporne fizičke aktivnosti, takmičarski, kontaktni i izometrijski sportovi.

Kod bolesnika sa Marfanovim sindromom, kao I kod onih sa bikuspidnim zalistkom i bolešću aortnog korena

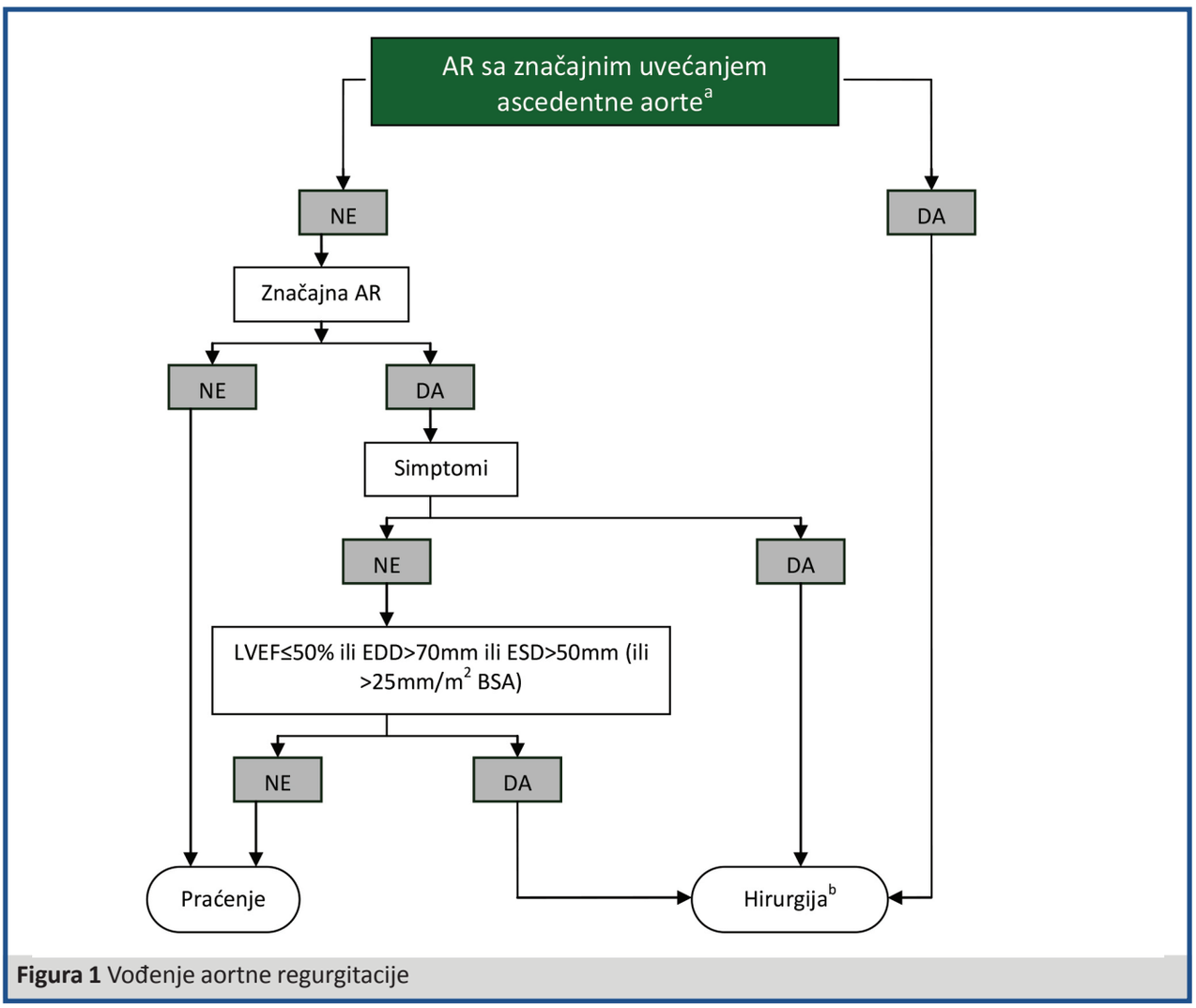


Figura 1 Vođenje aortne regurgitacije

AR – aortna regurgitacija, BSA – body surface area (telesna površina); LVEDD – enddijastolni dijametar leve komore, LVEF – ejekciona frakcija leve komore; LVESD – endsistolni dijametar leve komore, [a]Videti Tabelu 8 za definiciju b Hirurgija mora biti uzeta u obzir ukoliko se značajne promene dese tokom praćenja

treba proceniti porodični rizik pregledanjem bliskih rođaka prvog kolena.

4.6 Serijsko testiranje

Bolesnike sa umerenom do značajnom AR treba kontrolisati klinički jednom godišnje i ehokardiografski svake dve godine. Sve bolesnike sa normalnom funkcijom LV kod kojih je prvi put konstatovana značajna AR treba pregledati ponovo za 6 meseci. Ako se tada ustanovi da se dijametar LV i/ili EF značajno menja, ili bliži pragu za intervenciju kontrole treba nastaviti u šestomesečnim intervalima. Bolesnike sa stabilnim parametrima treba pratiti godišnje. Kod bolesnika sa dilatiranom aortom – naročito kod bolesnika sa Marfanovim sindromom ili bikuspidnim zalistkom – ehokardiografiju treba vršiti godišnje. MSCT ili bolje CMR treba vršiti kada se distalna aorta ne vizuelizuje dobro i/ili kada su indikacije za operaciju date na osnovu uvećanja aorte, a ne uvećanja i funkcije LV.

4.7 Posebne grupe bolesnika

Ako je značajna AR udružena sa značajnom MR, treba operisati oba zalistka.

Kod bolesnika sa umerenom AR, kod kojih je indikovana operacija mitralnog zalistka ili CABG, odluku da se operiše aortni zalistak treba doneti na osnovu porekla AR, godina starosti, pogoršanja funkcije LV i mogućnosti rekonstrukcije zalistka.

Detaljnije informacije o bolesnicima sa Marfanovim sindromom postoje u ESC preporukama o urođenim srčanim manama kod odraslih.[11]

5. Aortna stenoza

AS je najčešća valvularna mana u Evropi i Severnoj Americi. Uglavnom se prezentuje kao kalcifikovana aortna stenoza kod odraslih starijih bolesnika (2–7% populacije >65 god.)[1,2]

Sledeća najčešća etiologija koja je prisutna kod mlađe populacije je kongenitalna dok je reumatska AS izuzetno retka. Tretman visokorizičnih bolesnika je olakšan pojavom TAVI procedura.

5.1 Procena

Za procenu bolesnika je značajno pažljivo ispitivanje o simptomima (nedostatak vazduha u naporu, bol u

grudima, vrtoglavica, sinkopa). Mora se uzeti u obzir da bolesnik poriče simptome jer je nesvesno smanjio svoje aktivnosti.

Karakterističan sistolni šum privlači pažnju i zahteva dalju dijagnostiku. Šum može biti i blag i primarna prezentacija može biti SI. Za značajnu AS specifičan je nestanak drugog srčanog tona, mada taj znak nije senzitivan.[12]

Opšti principi za invazivnu i neinvazivnu dijagnostiku su kao što je navedeno u preporukama iz *Opštih komentara* (sekcija 3).

Specifičnosti vezane za AS su:

- Ehokardiografija je ključna dijagnostička metoda. Njom se potvrđuje prisustvo AS, procenjuje stepen kalcifikacije zalistka, funkcija LV i debljina zidova, potvrđuje prisustvo drugih bolesti zalistka ili aorte i omogućuju prognostičke informacije.

Dopler ehokardiografija je tehnika za procenu značajnosti AS (tabela 4).[15]

Transvalvularni gradijent zavisi od protoka i merenje površine ušća teoretski predstavlja idealan način. Ipak, u kliničkoj praksi, merenje aortnog ušća je zavisno od operatera i manje robusno nego procena gradijenta. Prema tome donošenje kliničke odluke ne može se zasnivati samo na veličini ušća zalistka, već u kombinaciji sa brzinom protoka, gradijentom pritiska, funkcijom LV, debljinom zidova, stepenom kalcifikacije zalistka, krvnim pritiskom i funkcionalnim statusom. Mada se površina aortnog ušća <1 cm^2 smatra značajnom, kritična stenoza je verovatnija sa ušćem <0.8 cm^2.[76] Kod bolesnika sa malom BSA koristi se granična vrednost od <0.6 cm^2/m^2.

Kada postoji normalan udarni volumen (tačnije transvalvularni protok) i kada je srednji gradijent <40 mmHg, malo je verovatno da postoji značajna AS. Kod postojanja malog protoka niski gradijenti pritiska mogu se naći i kod bolesnika sa značajnom AS (low flow-low gradient AS), mada će većina ipak imati visok gradijent. Do sada je ta pojava uglavnom utvrđena kod bolesnika sa lošom sistolnom funkcijom LV. Ipak, kod srednjeg gradijenta <40 mmHg mala površina ušća ne znači sigurno i značajnu AS zbog toga što se kod umerene do značajne stenoze valvula ne mora otvoriti potpuno, što rezultuje „funkcionalno malom površinom ušća" (pseudoznačajnom AS).[77] Od pomoći može biti nisko dozni dobutaminski ehokardiografski test. Kod stvarno značajne AS doći će samo do malog porasta u površini ušća (povećanje < 0.2 cm2 i ostaće <1.0 cm^2) sa povećanjem brzine protoka, ali će doći do značajnog povećanja gradijenta (srednji gradijent >40 mmHg), dok pseudoznačajna stenoza pokazuje samo mali porast u gradijentu, a značajan porast u veličini ušća.[22] Takođe, ovim testom može da se potvrdi prisustvo rezerve protoka, takođe nazvane kontraktilna rezerva (porast udarnog volumena >20 %), što ima prognostički značaj.[22,78]

U poslednje vreme predstavlja se novi entitet – „paradoksno nizak protok" (indeks udarnog volumena <35 ml/m^2), nizak gradijent (srednji gradijent <40 mmHg) AS sa očuvanom EF, tj. značajna AS kada je površina ušća <1.0 cm^2 , srednji gradijent <40 mmHg, uprkos očuvanoj EF.[76] Smatra se da se tipično javlja kod starih i da je povezana sa malom levom komorom, značajnom hipertrofijom zidova i dugogodišnjom hipertenzijom. Kod te grupe bolesnika je nejasna terapija. Takođe je pokazano da bolesnici koji imaju malu površinu ušća – ali nizak gradijent uprkos normalnoj EF – mogu imati zaista umerenu AS.[79] Mora se uzeti u obzir da često postoje drugi razlozi osim aortne stenoze za takvu kombinaciju parametara: prvo, doplerske mere mogu da potcene protok i tako stvore pogrešnu pretpostavku da postoji nizak protok;[15] drugo, osoba može biti veoma sitne građe;[15] treće, granične vrednosti za gradijent nisu potpuno konzistentne. Pokazano je da srednji gradijent od 40 mmHg više odgovara površini ušća od 0.8 cm^2 nego 1.0 cm^2.[76] Pre donošenja dijagnoze značajne aortne stenoze treba uzeti u obzir sve faktore koji mogu da utiču na ehokardiografski nalaz. To često može značiti uključenje CMR i kateterizacije. Kako se uglavnom radi o starijim bolesnicima sa hipertenzijom i drugim komorbiditetima procena često predstavlja problem čak i nakon potvrde hemodinamskih podataka. Hipertrofija i fibroza LV, kao i simptomi povećanih neurohormona, mogu biti najpre posledica hipertrofije LV. Takođe, ostaje nejasno kako isključiti pseudoznačajnu AS. Od pomoći može biti procena kalcifikacija MSCTom.[24]

Kada postoji hipertenzija procenu treba vršiti dok je bolesnik normotenzivan.[15]

Stres eho test omogućava prognostičke informacije kod asimptomatske značajne AS procenom porasta srednjeg gradijenta pritiska i promeni u funkciji LV sa vežbom.[21,80,81]

TEE se retko koristi za kvantifikaciju AS jer je planimetrija zalistka otežana kod prisustva kalcifikacija.[15] TEE, međutim, može pružiti korisne informacije o morfologiji mitralnog zalistka i ima sve veći značaj u proceni anulusa pre TAVI i tokom te procedure.[26,27,82]

- Testovi opterećenja su kontraindikovani kod simptomatskih bolesnika sa AS. Sa druge strane, indikovani su kod bolesnika sa asimptomatskom AS koji su fizički aktivni radi provociranja simptoma i stratifikacije rizika.[21,83] Ipak, dispnea u naporu je nespecifičan znak posebno kod starih bolesnika koji su i inače manje aktivni. Test opterećenja je bezbedan kod asimptomatskih bolesnika pod uslovom da ga izvodi iskusan lekar uz praćenje simptoma, promena u krvnom pritisku i/ili EKG promena.[21,83]
- MSCT i CMR daju dodatne informacije o ushodnoj aorti kada je uvećana. MSCT pruža informacije o veličini ušća i koronarnim kalcifikacijama što je od značaja za prognozu. MSCT je značajno sredstvo u proceni korena aorte, distribuciji kalcijuma, broja listića, ascedentne aorte i patologije perifernih arterija pre izvođenja TAVI.[26,27]

Mere aortnog anulusa dobijene različitim tehnikama se razlikuju, pa ih pažljivo treba interpretirati pre TAVI procedure[26]. Preporučuje se integrativni pristup.

CMR može biti koristan za detekciju i kvantifikaciju miokardne fibroze, dajući dodatne prognostičke informacije kod simptomatskih bolesnika bez CAD.[84]

- Kod asimptomatskih bolesnika natriuretski peptid može predvideti ishod i preživljavanje kod „low flow" AS bez simptoma i asimptomatske značajne AS.[85–87]

Tabela 9. Indikacije za zamenu aortnog zalistka kod aortne stenoze

	Klasa[a]	Nivo[b]	Refc
Bolesnici sa značajnom AS i bilo kojim simptomima vezanim za AS.	I	B	12,89,94
Bolesnici sa značajnom AS koji idu na aortokoronarni bajpas, operaciju ascedentne aorte, ili druge valvule.	I	C	
Asimptomatski bolesnici sa značajnom AS i sistolnom disfunkcijom LV (LVEF<50%) ukoliko nije usled drugog uzroka	I	C	
Asimtomatski bolesnici sa značajnom AS i patološkim testom opterećenja sa simptomima u naporu koji su jasno vezani za AS.	I	C	
Visokorizični bolesnici sa značajnom simptomatskom AS koji su podobni za TAVI, ali kod kojih se „kardiohirurški tim“ izjasnio da je operacija bolja opcija s obzirom na individualni rizik i anatomsku podobnost.	IIa	B	97
Asimptomatski bolesnici sa značajnom AS i nenormalnim testom opterećenja sa padom sistolnog pritiska.	IIa	C	
Bolesnici sa umerenom ASd koji idu na aortokoronarni bajpas , operaciju ascedentne aorte ili druge valvule.	IIa	C	
Simptomatski bolesnici sa „low flow low gradijent“ AS (<40 mmHg) sa normalnom EF nakon pažljive potvrde značajne AS.[e]	IIa	C	
AS sa niskim gradijentom (<40mmHg) I disfunkcijom LV sa kontraktilnom rezervom.f	IIa	C	
Asimptomatski bolesnici sa normalnom EF i nijednom od gore pomenutih abnormalnosti na testu opterećenja, ako je hirurški rizik nizak i postoji jedan od sledećih nalaza: - vrlo značajna AS definisana maksimalnom transvalvularnom brzinom >5.5m/s ili - značajnakalcifikacija zalistka i brzina progresije maksimalne transvalvularne brzine ≥0.3 m/s godišnje	IIa	C	
Simptomatski bolesnici sa značajnom AS „low flow low gradijent“ i disfunkcijom LV bez kontraktilne rezerve.	IIb	C	
Asimptomatski bolesnici sa značajnom AS, normalnom EF i ni jednom od gore pomenutih abnormalnosti na testu opterećenja, ako je hirurški rizik nizak i postoji jedan od sledećih nalaza: - Značajno uvećan nivo natriuretskog peptida potvrđen ponovljenim merenjima i bez drugog objašnjenja. - Porast srednjeg gradijenta u naporu za >20 mmHg. - Značajna hipertrofija LV u odsustvu hipertenzije.	IIb	C	

AS – aortna stenoza; BSA – body surface area (telesna površina); EF – ejekciona frakcija; EF – ejekciona frakcija; TAVI – transcateter aortic valve implantation (transkateterska implantacija aortnog zalistka), [a]Klasa preporuka, [b]Nivo dokaza, [c]Reference podržavaju klasu I (A+B) i IIa+IIb (A+B) preporuka, [d]Umerena aortna stenoza definisana kao površina ušća 1.0–1.5 cm^2 (0.6–0.9 cm^2/m^2BSA) ili srednji aortni gradijent 25–40 mmHg u prisustvu normalnih uslova protoka. Ipak potrebna je klinička procena, [e]Kod bolesnika sa malom površinom ušća, ali malim gradijentom uprkos očuvanoj EF. Objašnjenja za to (sem značajne AS) su česta i moraju biti pažljivo isključena. Vidi tekst (Procena aortne stenoze)

- Retrogradna kateterizacija LV se retko koristi, samo kada je neinvazivna procena nedovoljno informativna.

Konačno, kod ove grupe bolesnika najvažnije je traganje za komorbiditetima.

5.2 Prirodni tok

Kalcifikovana aortna stenoza je hronična progresivna bolest. Ima dug latentni period u kome su bolesnici asimptomatski.[88–91] Trajanje asimptomatske faze je individualno. Iznenadna srčana smrt je čest uzrok smrti kod simptomatskih bolesnika, ali je kod asimptomatskih retka. (<1 % godišnje), čak i kod veoma značajne AS.[88–91] Kod asimptomatskih bolesnika sa značajnom AS dvogodišnje preživljavanje bez neželjenih događaja se kreće od 20 % do preko 50 %.[88–91] Treba uzeti u obzir da se neki bolesnici operišu bez simptoma.

Kod asimptomatske aortne stenoze poznati su mnogi faktori rizika. Ti faktori su korisni u predviđanju preživljavanja bez neželjenih događaja. Ostalo je nejasno da li treba operisati bolesnike rano, pre pojave simptoma, u prisustvu ovih faktora rizika. Prediktori razvoja simptoma i lošeg ishoda kod asimptomatskih bolesnika su:

- klinički – starije doba, prisustvo ateroskleroze
- ehokardiografski – kalcifikacija zalistka, maksimalna brzina aortnog protoka,[88-91] EF,[90] brzina hemodinamske progresije,[89] porast gradijenta u naporu,[80,81] značajna hipertrofija LV,[92] abnormalnosti parametara tkivnog doplera sistolne i dijastolne funkcije LV.[87]
- test opterećenja – Provociranje simptoma testom opterećenja kod fizički aktivnih bolesnika, posebno mlađih od 70 godina, visoko je prediktivno za razvoj simptoma u sledećih 12 meseci. Pad arterijskog pritiska u naporu, pa i ST depresija imaju manji prognostički značaj nego simptomi u predviđanju nepovoljnog ishoda.[93]
- biomarkeri – povišen nivo natriuterskog peptida, mada precizna verdnost nije definisana.[85-87]

Brzo po pojavi simptoma nastupa nepovoljan ishod AS, sa stopom preživljavanja samo 10–50 % na 5 godina. Podaci o spontanom ishodu kod bolesnika sa niskim gradijentom i dobrom EF su i dalje kontroverzni.[79]

5.3 Rezultati intervencije

Zamena aortnog zalistka (ZAZ) je definitivna terapija za značajnu AS. Prema savremenim podacima operativni mortalitet zamene aortnog zalistka kod izolovane aortne stenoze je ~1–3 % kod bolesnika mlađih od 70 godina i 4–8 % kod starijih (tabela 7)[1,12,32–35,40,41,94–97] Sledeći faktori povećavaju rizik za operativni mortalitet: starije doba, komorbiditeti, ženski pol, viša funkcionalna klasa, hitna operacija, disfunkcija LV, plućna hipertenzija, udružena CAD, ranija operacija zalistka ili koronarni bajpas. Posle uspešne ZAZ značajno se popravljaju simptomi i kvalitet života. Kod starijih dugoročno preživljavanje je slično kao kod opšte populacije istog doba. Kod mladih postoji značajno poboljšanje u poređenju sa konzervativnom terapijom. Ipak, u poređenju sa opštom populacijom istog doba preživljavanje je niže. Faktori rizika za kasniju postoperativnu smrtnost su starost, komorbiditeti, značajni simptomi, disfunkcija LV, komorske aritmije, nelečena udružena koronarna bolest. Dodatno su moguće komplikacije vezane za samu protezu.

Hirurgija poboljšava i produžava život čak i kod bolesnika preko 80 godina starosti.[94–97]

Starost sama po sebi nije kontraindikacija za operaciju. Pored toga veliki broj povoljnih kandidata se i dalje ne upućuje na operaciju.[4,6]

Balon valvuloplastika je značajna kod pedijatrijskih bolesnika, ali kod odraslih ima ograničenu ulogu s obzirom da joj je efikasnost niska, stopa komplikacija visoka (>10 %) i restenoza i kliničko pogoršanje se javljaju za 6–12 meseci kod većine bolesnika šo na dugi rok ne poboljšava preživljavanje u odnosu na prirodan tok.[98]

Kod bolesnika sa visokim operativnim rizikom moguće je izvršiti TAVI (proceduralni uspeh >90%) koristeći transfemoralni, transapikalni ili ređe subklavijalni ili direktan transaortni pristup [97,99–107]. U odsustvu anatomskih kontraindikacija transfemoralni pristup je tehnika izbora u većini centara mada ne postoje podaci o prednosti jednog pristupa nad drugim. Slično ne postoje komparativni podaci o raspoloživim uređajima. 30-dnevni mortalitet je 5–15 %.[99–101,103–106] Najnačajnije komplikacije su: moždani udar (~1–5 %), potreba za pejsmejkerom (7 % za sistem koji se širi balonom i 40 % za samo-šireći);[99–103] i vaskularne komplikacije (do 20 %).[97–99]. Paravalvularna regurgitacija je česta mada uglavnom u tragu ili blaga kod većine bolesnika. Značajnija regurgitacija može imati uticaj na preživljavanje.[103–105] Približno 1-2 % bolesnika sa TAVI se upućuje na hitnu operaciju zbog životno ugrožavajućih komplikacija.[100]

TAVI daje hemodinamske rezultate koji su nešto bolji nego kod standardnih bioproteza.[97]

Jednogodišnje preživljavanje kod TAVI je 60–80 % i u mnogome zavisi od težine komorbiditeta.[97,99,102,103,105,107,108] Većina preživelih ima značajno poboljšanje kvaliteta života. Ipak trajnost ovih valvula još treba ispitati, mada su 3-5 godišnji rezultati obećavajući.[108]

Skorašnji izveštaj akademskog istraživačkog konzorcijuma za valvule nudi standardizovanu definiciju ishoda posle TAVI procedure, što će omogućiti tačnije poređenje pristupa i uređaja.[109]

Bolesnici koji nisu podobni za ZAZ imaju jasnu korist od TAVI u poređenju sa konzervativnim tretmanom što uključuje balon valvuloplastiku, kao što je pokazano randomizovanim istraživanjem (1-godišnji mortalitet 31 % nasuprot 51 % i značajno smanjenje simptoma sa manjim brojem hospitalizacija).[99] Prvo randomizovano istraživanje koje je poredilo ZAZ i TAVI kod visoko rizičnih ali operabilnih bolesnika pokazalo je da TAVI nije inferioran u smislu 1-godišnjeg preživljavanja (24.2 % vs 26.8 %), sa značajnim funkcionalnim poboljšanjem u obe grupe.[97] Analiza sekundarnih ishoda je pokazala sa da TAVI ima veći rizik od cerebrovaskularnih događaja i vaskularnih komplikacija i ima veću incidencu paravalvularnih regurgitacija, iako je većina blaga. Međutim, krvarenje i postoperativna AF su češće posle hirurgije. Interpretacija rezultata PARTNER istraživanja treba da uzme u obzir specifične indikacije i kontraindikacije za TAVI i stručnost hirurga i interventnih kardiologa uključenih centara.[97,99]

5.4 Indikacije za intervenciju

5.4.1 Indikacije za zamenu aortnog zalistka

Indikacije za ZAZ su prikazane u tabeli 9 i na slici 2.

Rana zamena zalistka se preporučuje kod svih simptomatskih bolesnika sa značajnom AS. Sve dok je srednji gradijent >40 mmHg ne postoji donja granica EF za operaciju.

Tretman bolesnika sa klasičnim „low flow low gradijent AS" (površina ušća <1 cm^2, EF <40 %, srednji gradijent <40 mmHg) je komplikovaniji. U slučaju kada je snižena EF dominantno usled povišenog naknadnog opterećenja (afterload), funkcija LV se obično popravlja posle operacije.[22,79,110] Nasuprot tome, ukoliko je primarni uzrok loše EF ožiljak posle ekstenzivnog infarkta miokarda ili kardiomiopatije, poboljšanje funkcije LV nakon ZAZ je nesigurno. Kod bolesnika sa niskim gradijentom i dokazanom očuvanom kontraktilnom rezervom savetuje se operacija.[22] Mada je kod bolesnika bez kontraktilne rezerve povećan operativni mortalitet, ZAZ poboljšava EF i klinički status i kod takvih bolesnika.[22,78,110] Konačna odluka treba da uzme u obzir kliničko stanje bolesnika (posebno prisustvo i obim komorbiditeta), stepen kalcifikacije zalistka, proširenost koronarne bolesti, izvodljivost revaskularizacije. Nedavno prepoznat entitet AS paradoksno niskog protoka i niskog gradijenta sa normalnom EF zahteva specijalnu pažnju zbog ograničenih podataka o prirodnom toku i ishodu nakon operacije.[76,79] Kod takvih slučajeva treba operisati samo kada postoje simptomi.

Kada postoji značajna asimptomatska aortna stenoza, postupak je i dalje nejasan. Poslednja istraživanja ne pružaju ubedljive podatke koji bi ukazivali na potrebu za ranom ZAZ, čak i kod veoma značajne AS.[88–91,111,112] Odluku da se asimptomatski bolesnik operiše treba doneti vrlo pažljivo poređenjem koristi i rizika.

Rana hirurgija je indikovana kod asimptomatskih bolesnika sa sniženom EF koja nije usled drugih uzroka ili kod onih sa padom arterijskog pritiska na testu opterećenja.[21, 83,90,93]

Treba operisati bolesnike sa niskim operativnim rizikom, sa normalnom tolerancijom napora i sledećim parametrima:

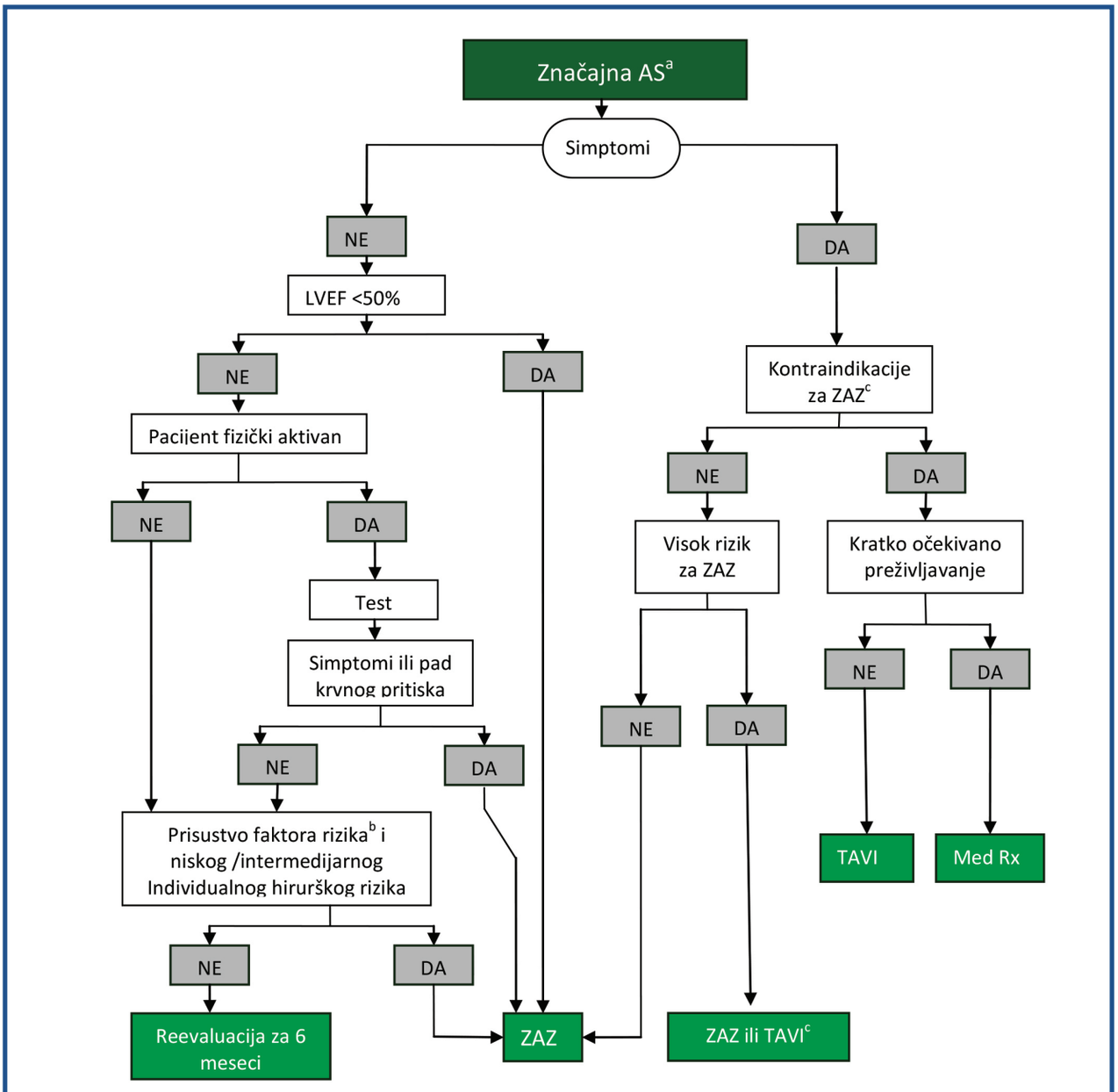


Figura 2. Lečenje značajne aortne stenoze. Vođenje bolesnika sa niskim gradijentom i niskom ejekcionom frakcijom je opisano u tekstu.

AS – aortna stenoza, ZAZ – zamena aortnog zalistka, BSA – body surface area (telesna površina), LVEF – ejekciona frakcija leve komore, Med Rx – farmakološka terapija, TAVI – transcateter aortic valve implantation (transkateterska implantacija aortnog zalistka), [a]Vidi tabelu 4 za definiciju značajne aortne stenoze, [b]Operaciju treba razmotriti (IIaC) ako je prisutan neki od faktora (maksimalna brzina >5.5 m/s); značajne kalcifikacije na zalistku+brzina progresije maksimalne transvalvularne brzine.

- veoma značajna AS sa maksimalnom brzinom >5.5 m/s,[91,112] ili
- kombinacija opsežnih kalcifikacija zalistka sa brzim porastom maksimalne brzine ≥0.3 m/s godišnje.[89]

Operaciju takođe treba planirati kod bolesnika sa niskim operativnim rizikom, sa normalnom tolerancijom napora i sledećim parametrima:

- značajno povišen BNP koji se ne može objasniti drugim uzrokom,[85-87]
- povećanje srednjeg gradijenta pritiska u naporu >20 mmHg[80,81] ili
- značajna hipertrofija LV bez dugogodišnje hipertenzije.[92]

Kod bolesnika bez ovih faktora rizika bolje je redovno kontrolisati bolesnike nego ih rano operisati.

5.4.2 Indikacije za balon valvuloplastiku

Balon valvuloplastiku treba koristiti kao most do ZAZ ili TAVI kod hemodinamski nestabilnih visokorizičnih bolesnika ili kod bolesnika sa simptomatskom značajnom AS koji moraju na hitnu nekardiološku operaciju (klasa preporuka IIb, nivo dokaza C). Balon valvuloplastika može biti i palijativna mera u izabranim slučajevima kada je zbog značajnih komorbiditeta kontraindikovana ZAZ, a TAVI nije opcija.

5.4.3 Indikacije za transkatetersku implantaciju aortnog zalistka

TAVI treba izvoditi u centrima sa dostupnom kardiohirurgijom. Odluku treba da donese „Kardiohirurški tim" koji procenjuje rizik za svakog bolesnika, kao i tehničku izvodljivost TAVI.[113]

Treba prepoznati eventualne kontraindikacije, kliničke i anatomske (tabela 10). Izabrani bolesnici treba da imaju očekivano trajanje života viće od 1 godine. Treba da imaju mogućnost da dobiju bolji kvalitet života uzimajući u obzir komorbiditete.

Prema sadašnjim podacima TAVI se preporučuje kod bolesnika sa značajnom simptomatskom AS koji su prema odluci kardiohirurškog tima nepodobni za klasičnu operaciju zbog značajnih komorbiditeta (tabela 11, shema 2).

Među visokorizičnim bolesnicima koji su kandidati za hirurgiju, odluku o operaciji treba doneti za svakog pojedinačno. TAVI treba razmotriti kao alternative hirurgiji kod onih bolesnika kod kojih je to predložio kardiohirurški tim, uzimajući u obzir prednosti i mane obe tehnike. Logistički EuroSCORE ≥20 % je predložen kao indikacija za TAVI, ali poznato je da EuroSCORE značajno precenjuje operativni mortalitet.[113] Upotreba STS scoring sistema >10 % može dati realističniju procenu operativnog rizika.[40] Sa druge strane fragilna aorta, istorija zračenja grudnog koša ili prolazni koronarni graftovi mogu činiti bolesnika manje podložnim ZAZ bez obzira na logistički EuroSCORE <20 % /STS skor<10 %. Kako ne postoji savršeni skor konačnu procenu rizika treba da da kardiohirurški tim uzimajući u obzir kombinaciju skorova.[113]

Prema dosadašnjim saznanjima kod bolesnika sa srednjim rizikom ne treba raditi TAVI. Ta tema ostaje otvorena.

5.5 Farmakološka terapija

Progresija degenerativne AS je aktivni proces, nalik aterosklerozi. Mada većina retrospektivnih izveštaja pokazuje korist od statina i ACE inhibitora randomizivana istraživanja stalno pokazuju da statini ne utiču na prognozu AS.[114,115.] Ne treba koristiti statine kod AS ako im je jedina svrha usporavanja bolesti. Sa druge strane, treba strogo redukovati faktore rizika za aterosklerozu, sledeći preporuke sekundarne prevencije ateroskleroze.[116]

Simptomatski bolesnici zahtevaju ranu intervenciju zato što nijedna farmakološka terapija ne menja prirodan tok bolesti. Ipak, bolesnici koji nisu kandidati za hirurgiju ili TAVI ili koji čekaju planiranu intervenciju mogu dobijati digoxin, diuretike, ACE inhibitore, ili ARB ako imaju simptome SI. Takođe, treba lečiti udruženu arterijsku hipertenziju.

Treba izbegavati hipotenziju i bolesnike treba redovno kontrolisati.

Značajno je održavanje sinusnog ritma.

5.6 Serijsko praćenje

Značajno je asimptomatske bolesnike edukovati o potrebi da se redovno kontrolišu kao i da prijave simptome kada se pojave. Testom opterećenja se utvrđuje preporučeni nivo aktivnosti. Praćenje je pre svega ehokardiografsko. Prati se hemodinamska progresija, funkcija i hipertrofija LV, kao i ushodna aorta. Interval praćenja treba odrediti na inicijalnom pregledu.

Asimptomatsku značajnu AS treba kontrolisati svakih 6 meseci. Prati se pojava simptoma, promena u toleranciji napora (ako su simptomi nejasni, uraditi test opterećenjem) i promene u eho parametrima. Može se pratiti i vrednost natriuretskog peptida.

Tabela 10. Kontraindikacije za transkatetersku implantaciju aortnog zalistka

Apsolutne kontraindikacije
Nepostojanje kardiohirurškog tima i kardiohirurgije u istoj ustanovi.
Kardiohirurški tim nije ustanovio da je TAVI prikladna zamena kardiohirurgiji.
Klinički
Procenjeno trajanje života <1 g Poboljšanje kvaliteta života nakon TAVI malo verovatno obzirom na komorbiditete Značajna bolest drugog zalistka koja veoma doprinosi bolesnikovim tegobama i može se tretirati samo hirurški
Anatomski
Neodgovarajuća veličina anulusa (<18 mm, >29 mm[a]).
Tromb u levoj komori.
Aktivni endokarditis.
Povećan rizik od zatvaranja ušća koronarne arterije (asimetrična kalcifikacija zalistka, mala udaljenost između anulusa i ušća koronarne arterije, mali aortni sinusi).
Plak sa mobilnim trombima u ushodnoj aorti ili luku.
Za transfemoralni/subklavijalni pristup: neadekvatan vaskularni pristup (veličina krvnog suda, kalcifikacije, tortuozitet).
Relativne kontraindikacije
Bikuspidni ili nekalcifikovan zalistak.
Koronarna bolest koja zahteva revaskularizaciju.
Hemodinamska nestabilnost.
LVEF<20 %.
Za transapikalni pristup: značajna plućna bolest, apeks nije dostupan.

ZAZ – zamena aortnog zalistka; LV – leva komora; LVEF – ejekciona frakcija leve komore; TAVI – transcateter aortic valve implantation (transkateterska implantacija aortnog zalistka), [a]Kontraindikacije za upotrebu sadašnjih uređaja

Tabela 11. Preporuke za korišćenje transkateterske implantacije aortnog zalistka

Preporuke	Klasa[a]	Nivo[b]	Ref[c]
TAVI treba da izvede multidisciplinarni kardiohirurški tim koji uključuje kardiologa, kardiohirurga i drugog specijalistu po potrebi.	I	C	
TAVI treba raditi samo u bolnicama koje imaju i kardiohirurgiju.	I	C	
TAVI je indikovan kod bolesnika sa značajnom simptomatskom AS koji nisu podobni za ZAZ po procerni kardiohirurškog tima i koji imaju šansu za poboljšanje kvaliteta života i imaju očekivano trajanje života više od godinu dana uzimajući u obzir komorbiditete.	I	B	99
TAVI treba razmotriti kod visokorizičnih bolesnika sa značajnom simptomatskom AS koji mogu biti podobni za operaciju, ali je kardiohirurški tim procenio da je bolja opcija TAVI uzimajući u obzir individualni rizik i anatomsku podobnost.	IIa	B	97

AS – aortna stenoza; ZAZ – zamena aortnog zalistka; TAVI – transcateter aortic valve implantation (transkateterska implantacija aortnog zalistka, [a]Klasa preporuka, [b]Nivo dokaza, [c]Reference podržavaju klasu I (A+B) i IIa+IIb (A+B) preporuka

Kada postoje značajne kalcifikacije, blaga i umerena AS kontrolišu se godišnje. Mladi bolesnici sa blagom AS bez značajnih kalcifikacija se kontrolišu na 2–3 godine.

5.7 Specijalna grupa bolesnika

Kombinovana ZAZ i CABG nosi veći rizik nego izolovana ZAZ.[32-35] Ipak ZAZ dugo nakon CABG takođe nosi značajan rizik. Mada nema randomizovanih prospektivnih istraživanja, podaci iz retrospektivnih istraživanja ukazuju da bolesnici kod kojih je indikovan CABG i koji imaju umerenu AS (srednji gradijent uz dobru funkciju LV 25-40 mmHg, površina ušća 1.0–1.5 cm^2) imaju korist od udružene ZAZ. Takođe je sugerisano da ako je starost bolesnika <70 godina i da je brzina progresije 5mmHg godišnje bolesnici mogu imati korist od zamene zalistka kod CABG ako je maksimalni gradijent iznad 30 mmHg.[117] Preporučuje se individualna procena uzimajući u obzir BSA, hemodinamske podatke, kalcifikaciju listića, brzinu progresije AS, očekivano trajanje života i komorbiditete, kao i individualan rizik od udružene operacije u odnosu na kasnu reoperaciju.

Bolesnicima sa značajnom simptomatskom AS i difuznom koronarnom bolešću koji ne mogu biti revaskularizovani ne treba uskratiti ZAZ bez obzira što su grupa visokog rizika.

Preporuka nekoliko istraživanja je da postoji potencijalna korist od perkutane koronarne intervencije umesto CABG kod bolesnika sa AS. Ipak raspoloživi podaci nisu dovoljni da preporuče taj pristup sem kod visokorizičnih bolesnika sa akutnim koronarnim sindromom ili kod bolesnika sa neznačajnom AS.

Izvodljiva je kombinacija TAVI i perkutane koronarne intervencije, ali je potrebno još podataka da bi se izveo zaključak o preporuci. Odluka da se primene te metode, kao i njihov redosled, donosi se za svakog bolesnika pojedinačno imajući u vidu kliničko stanje, koronarnu anatomiju i ugrožen miokard.

Kada postoji MR udružena sa značajnom AS, ona može biti precenjena u prisustvu velikog pritiska u komori i njen značaj treba proceniti pažljivo (vidi opšte komentare, sekcija 3). Sve dok su listići morfološki normalni (nema prolapsa, post-reumatskih promena ili znakova infektivnog endokarditisa), normalan dijametar mitralnog anulusa i normalna geometrija LV, nije potrebno operisati mitralni zalistak.

Udružena aneurizma/dilatacija aorte zahteva isti tretman kao kod AR (vidi sekciju 4).

Za kongenitalnu AS videti preporuke o urođenim manama kod odraslih.[11]

6. Mitralna regurgitacija

MR je druga najčešća bolest zalistaka u Evropi koja zahteva operaciju.[1] Dobri rezultati kod rekonstrukcije zalistka su nametnuli da se redefiniše terapija. Ovo poglavlje se, prema mehanizmu nastanka MR, bavi odvojeno primarnom i sekundarnom MR.[118] U retkim slučajevima kada postoje oba mehanizma, jedan od njih je dominantan i prema njemu se upravlja lečenje.

6.1 Primarna mitralna regurgitacija

Primarna MR obuhvata sve slučajeve kada postoji oštećenje mitralnog aparata. Smanjenje incidence reumatske groznice i produžen životni vek uticali su na to da degenerativna MR postane najčešća.[1,2,12] Endokarditisom se bave odvojene specifične preporuke ESC.[10]

6.1.1 Procena

Akutna mitralna regurgitacija

Akutna mitralna regurgitacija zbog rupture papilarnog mišića može biti uzrok akutnog plućnog edema ili šoka kod bolesnika sa akutnim infarktom miokarda. Klinički nalaz može biti obmanjujući: leziju potcenjuje tih ili nečujan šum i nalaz ehokardiografskog kolor doplera. Na dijagnozu može da ukaže postojanje hiperdinamskog stanja kod akutne SI. Hitna ehokardiografija je od najvećeg značaja.[12,119]

Akutnu MR može da izazove i infektivni endokarditis i trauma grudnog koša.

Hronična mitralna regurgitacija

Kliničkim pregledom se postavlja sumnja da postoji MR i koliko može biti značajna prema intenzitetu i trajanju sistolnog šuma, kao i prisustvu trećeg srčanog tona.[12]

Osnovni principi za invazivnu i neinvazivnu dijagnostiku su kao u preporukama navedenim u Opštim komentarima (sekcija 3).

Specifičnosti vezane za MR su:

- Ehokardiografija je osnovna metoda i njome se procenjuje značaj, mehanizam, mogućnost rekonstrukcije i posledice.[17]

Tabela 12. Indikacije za operaciju kod značajne primarne mitralne regurgitacije

	Klasa[a]	Nivo[b]	Ref[c]
Rekonstrukcija mitralnog zalistka je tehnika izbora kada se smatra da će biti trajna.	I	C	
Operacija je indikovana kod simptomatskih bolesnika sa LVEF>30 % i LVESD<55 mm.	I	C	127,128
Operacija je indikovana kod asimptomatskih bolesnika sa disfunkcijom LV (LVESD≥45 mm i/ili LVEF≤60 %).	I	B	
Operaciju treba razmotriti kod asimptomatskih bolesnika sa očuvanom funkcijom LV i novonastalom atrijalnom fibrilacijom ili plućnom hipertenzijom (sistolni plućni pritisak u miru>50 mmHg).	IIa	C	
Operaciju treba razmotriti kod asimptomatskih bolesnika sa očuvanom funkcijom LV, šansom za trajnu rekonstrukciju, niskim operativnim rizikom i prolapsom zalistka i LVESD≥40 mm.	IIa	C	
Operaciju treba razmotriti kod bolesnika sa značajnom disfunkcijom LV (LVEF<30 % i/ili LVESD>55 mm) koja je refraktorna na farmakološku terapiju sa velikom verovatnoćom za trajnu rekonstrukciju i malo komorbiditeta.	IIa	C	
Operaciju treba razmotriti kod bolesnika sa značajnom disfunkcijom LV (LVEF<30 % i/ili LVESD>55 mm) koja je refraktorna na farmakološku terapiju sa malom verovatnoćom za trajnu rekonstrukciju i malo komorbiditeta.	IIb	C	
Operaciju treba razmotriti kod asimptomatskih bolesnika sa očuvanom funkcijom LV, velikom verovatnoćom za trajnu rekonstrukciju, niskim hirurškim rizikom i: - dilatacijom leve pretkomore (volumni index ≥60 ml/m2BSA) i sinusnim ritmom, ili - plućnom hipertenzijom u naporu (SPAP≥60 mmHg u naporu).	IIb	C	

BSA – body surface area (telesna površina); LV – leva komora; LVEF – ejekciona frakcija leve komore; LVESD – endsistolni dijametar leve komore; SPAP – sistolni pritisak u arteriji pulmonalis, [a]Klasa preporuka, [b]Nivo dokaza, [c]Refence podržavaju klasu I (A+B) i IIa+IIb (A+B) preporuka

Kriterijumi za definisanje značajne MR su navedeni u tabeli 5. U proceni značajnosti MR se može koristiti više metoda. Treba napustiti planimetriju regurgitirajućeg mlaza; ta mera je loše reproducibilna i zavisi od više faktora. Tačnije je merenje širine vene kontrakte (*vena contracta*), najužeg dela regurgitirajućeg mlaza. Kada je izvodljivo, imajući na umu ograničenja, polje proksimalnog ubrzanja – PISA metoda (*Proximal isovelocity surfice area)* je metoda izbora za procenu volumena regurgitacije i EROA uzimajući u obzir poznata ograničenja. Konačna procena značajnosti zahteva integraciju dopler i morfoloških informacija i uklapanje tih nalaza sa veličinom LV, LP i plućnim pritiskom (tabela 5).[17]

TTE omogućava preciznu anatomsku definiciju različitih oštećanja. Opis se daje prema segmentnoj i funkcionalnoj anatomskoj podeli prema Carpentieru da bi se procenila izvodljivost rekonstrukcije zalistka. TTE takođe procenjuje dimenzije mitralnog anulusa.[17]

TEE se često koristi u pripremi za operaciju, mada je TTE, u iskusnim rukama, često dovoljan.[120] Svakako treba istaći da preoperativna procena valvule zahteva iskustvo.[17]

Intraoperativni TEE je značajan za procenu uspešnosti rekonstrucije mitralne valvule i omogućava trenutnu hiruršku korekciju ako je neophodno.

3D TEE može pružiti više informacija.[121] Posledice MR na veličinu srca se procenjuju ehokardiografski merenjem volumena LP, veličine i EF LV, sistolnog pritiska u plućnoj arteriji i funkcije RV.

- Određivanje funkcionalnog kapaciteta testom opterećenja može doprineti proceni.[122] U iskusnim rukama stress eho test služi za procenu promena u MR, sistolnom pritisku u plućnoj arteriji i funkciji LV u naporu.[21,123,124] Nove tehnike kao što su kardiopulmonalni test opterećenja, globalni logitudinalni strejn (meren metodom spekl trekinga) i promene u volumenima LV uzrokovane naporom, EF i globalni strejn mogu predvideti postoperativnu disfunkciju LV.[124]
- Kod MR je procenjivana i neurohumoralna aktivacija, nekoliko istraživanja je ukazalo na BNP kao marker u predikciji ishoda. Granična vrednost od ≥105pg/ml je dobijena u derivacionoj kohorti i kasnije potvrđena u validacionoj kohorti. Identifikuje asimptomatske bolesnike u riziku da dobiju SI, disfunciju LV ili da umru tokom srednjeročnog praćenja.[125] Nizak nivo BNP ima negativnu prediktivnu vrednost i pomaže u praćenju asimptomatskih bolesnika.[126]

6.1.2 Prirodni tok

Akutna MR se loše toleriše i zahteva intervenciju. Kod bolesnika sa rupturom horde stanje se može stabilizovati. Ipak, ako se ne operiše ima nepovoljan prirodni tok usled razvoja plućne hipertenzije.

Kod asimptomatske značajne hronične MR procenjen petogodišnji mortalitet zbog bilo kog uzroka, srčanog uzroka i srčanih događaja (smrt zbog srčanog uzroka, HF ili novonastale AF lečene medikamentno) bila je 22+3 %, 14+3 %, i 33+3 % po redu.[118]

Osim simptoma prediktori lošeg ishoda su, starost, AF, značajnost MR (naročito EROA), plućna hipertenzija, dilatacija LP, povećan endsistolni dijametar LV i loša EF.[118,127,133]

6.1.3 Rezultati operacije

Uprkos odsustva randomizovanog poređenja rezultata zamene i rekonstrukcije zalistka, široko je prihvaćeno da je, ukoliko je izvodljivo, bolje vršiti rekonstrukciju zalistka kod teške MR. U poređenju sa zamenom rekonstrukcija ima manji perioperativni mortalitet, bolje preživljavanje, bolje očuvanje funkcije LV i niži dugoročni morbiditet (tabela 7).

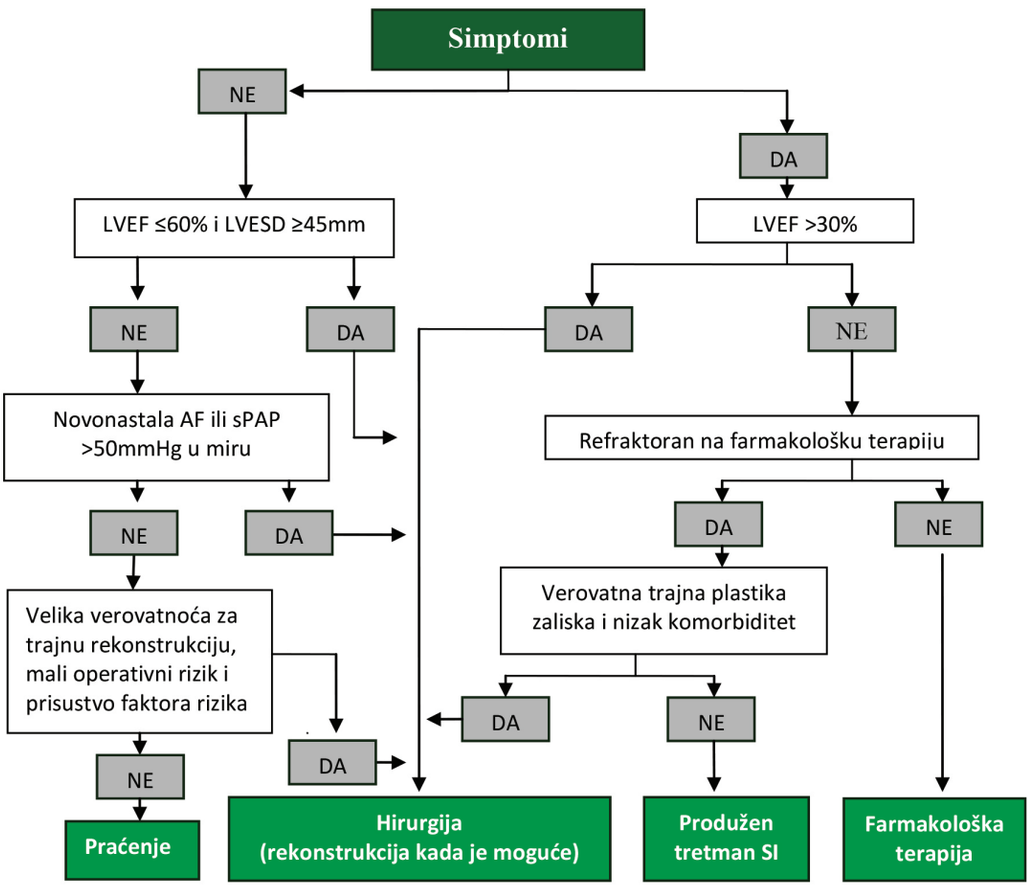


Figura 3. Lečenje značajne hronične primarne mitralne regurgitacije

AF – atrijalna fibrilacija; SI – srčana insuficijencija; LVEF – ejekciona frakcija leve komore; LVESD – endsistolnni dijametar leve komore; SPAP – sistolni pritisak u plućnoj arteriji, [a]Kada postoji velika verovatnoća trajne rekontrukcije zalistka pri niskom riziku, rekonstrukciju zalistka treba razmotriti (IIaC) kod bolesnika sa prolapsom zalistka i LVESD≥40 mm; rekonstrukciju zalistka treba razmotriti (IIbC) ako je prisutan neki od faktora: volumen leve pretkomore ≥60 ml/m^2 BSA i sinusni ritam ili plućna hipertenzija u naporu (SPAP≥60 mmHg), [b]Produženo lečenje SI podrazumeva sledeće: srčana resinhronizaciona terapija; mehaničke ventrikularne potporne pumpe, srčani bezbednosni uređaji; transplantacija srca.

Osim simptoma, najbolji prediktori postoperativnog ishoda su starost, AF, preoperativna funkcija LV, plućna hipertenzija i mogućnost rekontrukcije zalistka. Najbolji rezultati se dobijaju kod bolesnika sa preoperativnom EF>60%. Ranije je bilo široko prihvaćeno da je granična vrednost za kod mlatećeg mitralnog listića (*flail leaflet)* ESDLV 45 mm, dok je LVESD≥40 mm (≥22 mm/BSA) povezan sa povećanim mortalitetom ukoliko se leči samo konzervativno.[131] Kao dodatak inicijalnim merenjima praćenje promena dimenzija LV i sistolne funkcije takođe treba uzeti u obzir kada se odlučuje o operaciji, mada je potrebno još validacije.[133]

Od posebnog interesa je mogućnost trajne rekonstrukcije mitralnog zalistka. Degenerativno izmenjen mitralni zalistak sa segmentnom prolapsom zalistka može biti uspešno rekonstruisan sa niskim rizikom za reoperaciju. Nisu dobri rezultati reparacije kod reumatskih lezija, opširnog prolapsa zalistka i MR sa kalcifikacijama zalistka ili anulusa.[134] Sve je veća stručnost hirurga u rekonstruisanju zalistaka.[135]

Bolesnike podobne za rekonstrukciju treba operisati u centrima sa iskustvom i velikom stopom uspešnih operacija.[32-35,44,135]

Kada rekonstrukcija nije moguća, indikovana je zamena zalistka sa očuvanjem subvalvularnog aparata.

6.1.4 Perkutane intervencije

Razvijene su kateterske intervencije kojima se MR koriguje perkutano. Jedina koja je ispitana kod organske MR je –edge to edge" procedura. Podaci iz studije EVEREST (Endovascular Valve Edge-to Edge Repair Study)[136] i rezultati registara u Evropi[137] i SAD sugerišu da MitraClip procedura ima procenat uspešnosti oko 75 % (postproceduralnu MR ≤2+), sigurna je i dobro je tolerišu čak i bolesnici u teškom opštem stanju. Procenat onih koji prežive godinu dana bez operacije mitralnog zalistka i bez značajne MR je oko 55 %. Procedura je manje efektivna u redukciji MR od operacije mitralnog zalistka. Bolesnici su praćeni do 2 godine (Studija EVEREST II). Kod 20 % bolesnika je bila potrebna reintervencija tokom prve godine. Primenljivost procedure je ograničena time što moraju biti zadovoljeni precizni ehokardiografski kriterijumi da bi bolesnik bio podoban.[136] U slučaju neuspešne klip procedure nekada je moguća rekonstrukcija zalistka, mada je zamena potrebna kod oko 50% bolesnika.

6.1.5 Indikacije za intervenciju

Urgentna hirurgija je indikovana kod bolesnika sa akutnom značajnom MR. Ruptura papilarnog mišića zahteva hitnu operaciju nakon hemodinamske stabilizacije koja se postiže intraortnom balon pumpom, pozitivnim inotropnim agensima i kada je moguće vazodilatatorima. Operacija u većini slučajeva podrazumeva zamenu zalistka.[119]

Indikacije za operaciju kod značajne hronične primarne MR su prikazane u tabeli 12 i slici 3.

Odluka da se valvula rekonstruiše ili zameni zavisi od anatomije zalistka, stručnosti hirurga i stanja bolesnika. Operacija je indikovana kod bolesnika koji imaju simptome usled hronične MR, ali nemaju kontraindikacija za operaciju.

Kod EF<30 % trajna hirurška rekonstrukcija može poboljšati simptome, mada je efekat na preživljavanje uglavnom nepoznat. U takvoj situaciji odluka da se operiše zavisi od komorbiditeta, odgovora na farmakološku terapiju, mogućnosti uspešne rekonstrukcije.

Kandidati za perkutanu „edge to edge" proceduru su bolesnici sa simptomatskom značajnom primarnom MR koji ispunjavaju eho kriterijume,a od strane kardiohirurškog tima su proglašeni inoperabilnim i imaju očekivano trajanje života preko 1 godine. (preporuka klasa IIb, nivo dokaza C).

Lečenje asimptomatskih bolesnika je kontroverzno kako ne postoje randomizovane studije; ipak, asimptomatske bolesnike sa značajnom MR treba operisati, posebno ako je izvodljiva rekonstrukcija zalistka.[138,139]

Kod bolesnika sa znacima disfunkcije LV (EF≤60 % i/ili ESDLV≥45 mm), indikovana je operacija čak i kada je velika verovatnoća zamene zalistka. Kod bolesnika sitne građe treba koristiti manje vrednosti ESDLV.

Kod očuvane funkcije LV treba planirati operaciju u slučaju pojave AF ili plućne hipertenzije (sistolni pritisak u plućnoj arteriji >50 mmHg).[47]

Rezultati skorašnjih prospektivnih istraživanja ukazuju na indikacije za operaciju kod bolesnika sa niskim operativnim rizikom kada postoji mogućnost za rekonstrukciju zalistka:

- prolaps zalistka i ESDLV ≥40 mm (≥22 mm/m^2 kod bolesnika sitne građe)[131]
- sistolni plućni pritisak>60 mmHg u naporu,[21,123] bolesnik u sinusnom ritmu sa značajnom dilatacijom leve pretkomore (volumni indeks ≥60 ml/m^2 BSA)[132]

Druge asimptomatske bolesnike treba pratiti do pojave simptoma ili dok se ne dostignu ranije preporučene granične vrednosti. Takav pristup podrazumeva redovno i pažljivo praćenje.[138]

Kod bolesnika kod kojih postoji sumnja u izvodljivost rekonstrukcije zalistka potrebno je pažljivo praćenje. U ovoj grupi operativni rizik i/ili komplikacije zbog veštačkog zalistka prevažu prednosti operacije u ranom stadijumu. Njih treba pratiti do trenutka kada se pojave simptomi ili objektivni znaci disfunkcije LV.

Kada se ispune uslovi za operaciju prema preporukama treba je izvršiti u roku od 2 meseca jer je pojava čak i blagih simptoma pre operacije povezana sa pogoršanjem srčane funkcije nakon operacije.[139,140]

Konačno nedostaju podaci o koristi od operacije kod bolesnika sa prolapsom mitralnog zalistka, očuvanom funkcijom LV i rekurentnim komorskim aritmijama uprkos terapiji.

6.1.6 Farmakološka terapija

Kod akutne mitralne regurgitacije smanjenje pritisaka punjenja se postiže nitratima i diureticima. Na nitroprusid smanjuje naknadno opterećenje *(afterload)* i frakciju regurgitacije kao i intra-aortna balon pumpa. Inotropne agense i intraaortnu balon pumpu treba uključiti u slučaju hipotenzije.

Nema dokaza da su vazodilatatori (uključujući i ACE inhibitore) korisni kod hronične MR bez SI i ne treba ih primenjivati kod ove grupe bolesnika. Međutim, kada dođe do SI, ACE inhibitori su korisni i treba ih primeniti kod bolesnika sa značajnom MR i simptomima koji nisu kandidati za operaciju ili kod kojih postoje simptomi i nakon operacije. Moguće je imati korist i od beta blokatora i spironolaktona.[13]

6.1.7 Serijsko testiranje

Asimptomatske bolesnike sa umerenom MR i očuvanom funkcijom LV treba kontrolisati klinički godišnje, a ehokardiografski jednom u dve godine. Asimptomatske bolesnike sa značajnom MR i očuvanom funkcijom LV treba kontrolisati klinički na 6 meseci, a ehokardiografski godišnje. Interval praćenja treba da je kraći ukoliko se ne raspolaže rezultatima od ranije i ukoliko se pokaže da postoji brza progresija. Bolesnike treba savetovati da odmah prijave bilo koju promenu stanja.

6.2 Sekundarna mitralna regurgitacija

Kod sekundarne MR koja se još naziva i „funkcionalna", listići i horde su normalne strukture i MR nastaje zbog geometrijske distorzije subvalvularnog aparata koja nastaje kod uvećanja LV i remodelovanja kod idiopatske kardiomiopatije i CAD. Sekundarna MR se često naziva i ishemijska iako to ne mora da znači da postoji ishemija miokarda. Dakle, sekundarna MR nije primarna bolest zalistka, već nastaje usled zatezanja (apikalno i lateralno pomeranje papilarnih mišića, dilatacija anulusa) i smanjenih sila zatezanja, usled disfunkcije LV (smanjena kontraktilnost i/ili disinhronija LV).[12,17]

6.2.1 Procena

Kod hronične sekundarne MR šum je često blag i njegov intenzitet nije povezan sa značajnošću MR. Ishemijska MR je dinamsko stanje i njena značajnost varira od uslova punjenja, hipertenzija, farmakološka terapija, vežbanje. Dinamska komponenta se može proceniti testom opterećenja. Zbog povećanog plućnog vaskularnog pritiska može doći do akutnog plućnog edema.[141]

Ehokardiografski pregled je koristan za dijagnozu MR i diferencijaciju primarne od sekundarne kod bolesnika sa koronarnom bolešću i SI.

Nakon infarkta miokarda i kod bolesnika sa SI treba raditi ehokardiografski pregled da bi se ustanovila i kvantifikovala eventualna MR. Kao kod primarne MR planimetrija regurgitirajućeg mlaza precenjuje značajnost ishemijske MR i loše je reproducibilna: širina *vene contracte* daje bolju procenu. Kod sekundarne MR se

koriste niže granične vrednosti za značajnost (20 mm^2 ROA i 30 ml za volume regurgitacije(tabela 5).[17,118,142] Procena sistolne funkcije LV je otežana prisustvom MR.

Ishemijska MR je dinamsko stanje: u proceni ima značaja test opterećenja. Ehokardiografska kvantifikacija tokom testa opterećenja je izvodljiva, omogućava demonstraciju dinamskih karakteristika i ima prognostički značaj. Povećanje EROA≥13 mm^2 je povezano sa značajnim porastom relativnog rizika od smrti i hospitalizacija zbog srčane dekompenzacije.[143] Ostaje da se utvrdi prognostički značaj testa opterećenja u predviđanju rezultata operacije. Prognostički značaj dinamske MR nije obavezno isti kao značaj sekundarne MR zbog idiopatske kardiomiopatije.

Za upotpunjavanje dijagnoze značajna je procena stanja srčanih krvnih sudova i mogućnost revaskularizacije.

Kod bolesnika sa niskom EF obavezno je utvrditi prisustvo i obim vijabilnosti miokarda jednom od raspoloživih tehnika (dobutaminski stress eho test, SPECT, PET, CMR).

Kod bolesnika kod kojih se vrši revaskularizacija miokarda odluku da se MR operiše ili ne operiše treba doneti pre operacije zato što opšta anestezija umanjuje MR. Nekada je u operacionoj sali potrebno menjati prethodno opterećenje (*preload*) i naknadno opterećenje (*afterload*) radi procene MR.[144]

6.2.2 Prirodan tok

Bolesnici sa hroničnom ishemijskom MR imaju lošu prognozu.[118,142]. Prisustvo značajne CAD i disfunkcije LV ima prognostički značaj. Doprinos MR lošoj prognozi nije sasvim jasan. Svakako povećanje MR je povezano sa lošim ishodom.[142]

O bolesnicima sa sekundarnom MR koja nije ishemijske etiologije zna se manje[145] i teško je sprovesti preciznu analizu. Sprovedeno je nekoliko istraživanja na malim serijama bolesnika. Neke studije su pokazale nezavisnu povezanost značajne MR i loše prognoze.

6.2.3 Rezultati operacije

Operacija zbog sekundarne MR ostaje izazov. Operativni mortalitet je veći nego kod primarne MR i dugoročna prognoza je gora zbog uglavnom značajnih komorbiditeta (tabela 7). Kod bolesnika sa ishemijskom MR, indikacije za operaciju i procedura izbora ostaju uglavnom nejasni jer nedostaju dokazi da operacija produžava život i zbog male uspešnosti rekontrukcije zalistka.[146] Većina istraživanja pokazuje da se značajna MR uglavnom ne poboljšava revaskularizacijom i da prisustvo rezidualne MR nosi povećanu smrtnost. Uticaj operacije zalistka na smrtnost ostaje nejasan s obzirom da nema randomizovanih istraživanja da bi se izveli zaključci.[147] Nije pokazan povoljan uticaj na dugoročnu prognozu nakon hirurške korekcije sekundarne MR.[148,149]Jedino randomizovano istraživanje koje je poredilo CABG i CABG sa rekonstrukcijom zalistka kod bolesnika sa umerenom MR nije dizajnirano da analizira efekat na preživljavanje. Pokazalo je da rekonstrukcija zalistka u kratkom roku poboljšava funkcionalnu klasu, EF i dijametar leve komore.[150]

Kada je indikovana operacija zalistka postoji trend da se radi anuloplastika čvrstim prstenom što je vezano sa malim operativnim rizikom, mada nosi rizik od povratka MR.[151,152] Ova hirurška tehnika se koristi i kod MR usled kardiomiopatije.[153]

Kod implantacije rigidnog prstena zbog sekundarne MR postoje mnogi preoperativni prediktori rekurentne MR koji su pokazatelji zatezanja zalistka i povezali su sa lošom prognozom. [enddijastolni dijametar LV>50 mm, ugao zadnjeg mitralnog listića >45˚, ugao distalnog prednjeg listića >25˚, sistolna površina zatezanja *(tenting area)* >25 cm^2, koaptaciona distanca (distanca između anularne ravni i tačke koaptacije)>10 mm, endsistolna interpapilarna distanca >20 mm, sistolni index sferičnosti>0.7].[152] Prognostičku vrednost ovih parametara treba dalje potvrditi. Nakon operacije promenjena geometrija u blizini papilarnih mišića je povezana sa vraćanjem MR.

Preoperativno potvrđena značajna vijabilnost je prediktor dobrog ishoda kod istovremene operacije mitralnog zalistka i CABG.[154]

Ostaje nejasno da li restriktivna anuloplasika može da proizvede značajnu mitralnu stenozu.

Nijedno sprovedeno istraživanje nije poredilo rekonstrukciju i zamenu. U najkompleksnijim rizičnim slučajevima nema razlike u preživljavanju. Skorašnja meta analiza retrospektivnih istraživanja ukazuje na bolje preživljavanje nakon rekonstrukcije nego nakon zamene.[155] Kod bolesnika sa preoperativnim prediktorima povratka MR postoji nekoliko tehnika kojima se procenjuje subvalvularno zatezanje i treba ih razmotriti kao dodatak anuloplastici.[156] Skorašnje randomizovano istraživanje koje je obuhvatilo bolesnike kojima je rađena revaskularizacija i reoblikovanje LV pokazalo je poboljšano preživljavanje i smanjenje velikih neželjenih događaja.[157] Dobijeni su bolji rezultati nego kod sekundarne neishemijske MR.

6.2.4 Perkutane intervencije

Istraživanje na malom broju bolesnika u istraživanju EVEREST, kao i opservaciona istraživanja sugerišu da je perkutana „edge to edge" procedura izvodljiva kod bolesnika sa sekundarnom MR kada nema značajnog zatezanja i može kratkoročno da poboljša funkcionalno stanje i funkciju LV.[136,137] Potrebno je sprovesti randomizovana istraživanja na većim serijama sa dužim praćenjem. Podaci o anuloplastici koronarnog sinusa su ograničeni i povučena je upotreba prvobitnih instrumenata.[158]

6.2.5 Indikacije za intervenciju

Zbog heterogenosti podataka koji se tiču sekundarne MR, nije uvek jasno koje je lečenje najbolje (tabela 13).

Značajnu MR treba korigovati sa operacijom revaskularizacije.

Kod simptomatskih bolesnika sa značajnom sekundarnom MR i značajno sniženom sistolnom funkcijom koji ne mogu biti revaskularizovani ili imaju kardiomiopatiju ostaje otvoreno pitanje izolovane operacije mitralnog zalistka.

Kod bolesnika bez komorbiditeta može se operisati zalistak da bi se odložila ili izbegla transplantacija. Kod drugih je bolja opcija optimalna farmakološka terapija. U slučaju pogoršanja mere su srčana resinhranizaciona terapija; mehaničke ventrikularne potporne pumpe, srčani bezbednosni uređaji; transplantacija srca.

Tabela 13. Indikacije za operaciju mitralnog zalistka kod hronične sekundarne mitralne regurgitacije.

	Klasa[a]	Nivo[b]
Operacija je indikovana kod bolesnika sa značajnom MR[c] koji idu na CABG i imaju LVEF>30 %.	I	C
Operaciju treba razmotriti kod bolesnika sa umerenom MR koji idu na CABG[d].	IIa	C
Operaciju treba razmotriti kod simptomatskih bolesnika sa značajnom MR, LVEF<30 %, mogućnošću revaskularizacije i dokazom vijabilnosti.	IIa	C
Operaciju treba razmotriti kod bolesnika sa značajnom MR, LVEF>30%, koji ostaju simptomatski uprkos optimalnom lečenju (uključujući i CRT ako je potrebno) i imaju malo komorbiditeta, kada nije indikovana revaskularizacija.	IIb	C

CABG – koronarni arterijski bajpas grafting; CRT – kardijalna resinhronizaciona terapija; LVEF – ejekciona frakcija leve komore; MR – mitralna regurgitacija; SPAP-sistolni pritisak u arteriji pulmonalis, [a]Klasa preporuka, [b]Nivo dokaza, [c]Prag značajnosti (EROA≥20 mm^2, R Vol>30 ml) različit je od primarne MR i zasniva se na mogućnosti da prognozira loš ishod: videti tabelu 5, [RV]ada je moguć stress-ehokardiografski test, razvoj dispnee i povećanje značajnosti MR povezane sa plućnom hipertenzijom su dalji podsticaj za operaciju.

Perkutana mitral klip procedura je indikovana kod bolesnika sa značajnom sekundarnom MR koja je simptomatska i pored optimalne terapije (što uključuje i CRT), koja ispunjava eho kriteriume, od strane kardiohirurškog tima je proglašena inoperabilnom i koji imaju očekivano trajanje života duže od 1 godine (klasa preporuka IIb, nivo dokaza C) .

Lečenje umerene ishemijske MR kod bolesnika koji idu na CABG je i dalje otvorena tema. Kod takvih slučajeva metoda izbora je valvuloplastika. Kod bolesnika sa niskom EF operaciji mitralnog zalistka se pristupa kada postoji vijabilnost miokarda i kada nema značajnih komorbiditeta. Ako je moguće, treba uraditi stress eho test. Dispnea uzrokovana naporom i značajno povećanje intenziteta MR, kao i povećanje sistolnog pritiska u arteriji pulmonalis upućuju na potrebu kombinovane operacije.

Nema podataka koji bi ukazivali na potrebu da se blaga MR operativno koriguje.

6.2.6 Farmakološko lečenje

Optimalna farmakološka terapija je obavezna. Treba da bude prvi korak u lečenju svih bolesnika sa sekundarnom MR i u skladu sa preporukama o lečenji SI.[13] To uključuje ACE inhibitore i beta blokatore, sa dodatkom antagonista aldosterona u prisustvu SI. Diuretici su potrebni kod prisustva viška tečnosti. Nitrati se koriste kod izražene dispnee, sekundarno zbog velike dinamske komponente.

Indikacije za resinhronizacionu terapiju treba da su u skladu sa referentnim preporukama.[13] Kada postoji dobar odgovor, CRT može smanjiti MR povećanjem sila zatvaranja i resinhronizacijom papilarnih mišića.[159] Dalje smanjenje MR i njene dinamske komponente se javlja uslad smanjenja sila zatezanja kod reverznog remodelovanja LV.

7. Mitralna stenoza

Reumatske groznice, koja je najčešnji uzročnik MS, sve je manje u industrijalizovanim zemljama; ipak, MS ostaje značajan uzrok morbiditeta i mortaliteta širom sveta.[1,3] Perkutana mitralna komisurotomija (PMC) je značajno uticala na lečenje reumatske mitralne stenoze.

7.1 Procena

Bolesnici sa mitralnom stenozom mogu biti bez simptoma godinama, a onda početi da se postepeno zamaraju. Dijagnoza se najčešće postavlja fizičkim pregledom, rendgenom grudnog koša, EKG nalazom i ehokardiografijom.

Opšti principi za invazivno i neinvazivno ispitivanje su prema preporukama koje su navedene u Opštim komentarima (sekcija 3).[12]

Specifičnosti vezane za MS su:

- Ehokardiografija je osnovna metoda za procenu značajnosti i posledica MS, kao i opsega anatomske lezije.
  Površinu mitralnog ušća treba proceniti planimetrijom i metodom poluvremena pada pritiska. Metode su komplementarne.
  Kada je izvodljiva, planimetrija je metoda izbora posebno odmah nakom PMC. Jednačinu kontinuiteta i PISA metodu treba koristiti kada su potrebne dodatne procene. Merenje srednjeg gradijenta je veoma zavisno od frekvence i protoka, ali je značajno u proveri značajnosti, posebno kod bolesnika u sinusnom ritmu. MS obično ne daje simptome u miru ukoliko je površina ušća >1.5 cm^2 (tabela 4)[15]
  Sveobuhvatna procena morfologije zalistka je važna u planiranju lečenja. Osmišljeni su scoring sistemi za procenu podobnosti za operaciju uzimajući u obzir zadebljanje zalistka, mobilnost, kalcifikacije, subvalvularni deformitet i komisuralna područja.[15,160,161]
  Ehokardiografijom se takođe procenjuje pritisak u plućnoj arteriji, udružena MR, udružena bolest zalistka i veličina leve pretkomore. S obzirom da je česta udruženost MS sa oboljenjem drugih zalistaka, obavezna je pažljiva procena trikuspidnog i aortnog zalistka.
  TTE obično pruža dovoljno informacija.
  TEE se koristi za isključenje postojanja tromba u levoj pretkomori pre PMC ili nakon embolijske epizode, ako TTE ne pruža dovoljno informacija ili u izabranim slučajevima za vođenje procedure.
  3DE poboljšava porcenu morfologije zalistka, (posebno vizuelizaciju komisura),[162] omogućava veću tačnost i reproduktivnost planimetrije i može se koristiti za navođene (TEE) i praćenje (TEE) PMC kod teških slučajeva.
- Stres test je indikovan kod asimptomatskih bolesnika ili simptomatskih koji su u suprotnosti sa značajnošću MS.

Dobutaminski ili bolje stress eho test fizičkim opterećenjem može pružiti dodatne informacije procenom promena u mitralnom gradijentu i plućnim pritiscima.21

Tabela 14. Indikacije za perkutanu mitralnu komisurotomiju kod mitralne stenoze sa površinom ušća ≤1,5 cm^2

	Klasa[a]	Nivo[b]	Ref[c]
PMC je indikovana kod simptomatskih bolesnika sa povoljnim karakteristikama.	I	B	160, 170
PMC je indikovana kod simptomatskih bolesnika sa kontraindikacijama ili visokim rizikom za operaciju.	I	C	
PMC treba razmotriti kao inicijalni tretman kod simptomatskih bolesnika sa nepovoljnom anatomijom, ali bez nepovoljnih kliničkih karakteristika[d].	IIa	C	
PMC treba razmotriti kod asimptomatskih bolesnika bez nepovoljnih karakteristika[d] i - Visok tromboembolijski rizik (anamneza embolije, gust spontani kontrast u levoj pretkomori, skora ili paroksizmalna atrijalna fibrilacija) i/ili - Visok rizik od hemodinamske dekompenzacije (sistolni plućni pritisak >50mmHg u miru, potreba za velikom nesrčanom operacijom, želja za trudnoćom).	IIa	C	

PMC – perkutana mitralna komisurotomija, NYHA – New York Heart association, [a]Klasa preporuka, [b]Nivo dokaza, [c]Reference podržavaju klasu I (A+B) i IIa+IIb (A+B) preporuka, [d]Nepovoljne karakteristike za perkutanu mitralnu komisurotomiju mogu biti definisane prisustvom nekih od sledećih faktora.
- Kliničke karakteristike : starost, ranija komisurotomija, NYHA klasa IV, permanentna atrijalna fibrilacija, značajna plućna hipertenzija.
- Anatomske karakteristike: echo score >8, Cormier score 3 (kalcifikacije mitralnog zalistka bilo kog opsega viđeno na fluoroskopiji), vrlo mala površina mitralnog ušća, značajna trikuspidna regurgitacija

Tabela 15. Kontraindikacije za perkutanu mitralnu kommisurotomiju

- Površina mitralnog ušća >1.5cm2
- Tromb u levoj pretkomori
- Više nego blaga mitralna regurgitacija
- Značajne ili bikomisuralne kalcifikacije
- Odsustvo komisuralne fuzije
- Značajna udružena bolest aortnog zalistka, ili značajna kombinovana trikuspidna stenoza i regurgitacija
- Udružena koronarna bolest koja zahteva hirurgiju

7.2 Prirodan tok

Kod asimptomatskih bolesnika desetogodišnje preživljavanje je dobro, progresija je često varijabilna sa naglim pogoršanjem koje može biti uzrokovano trudnoćom ili komplikacijama kao što su AF ili embolizacija.[163] Simptomatski bolesnici imaju lošu prognozu bez intervencije.[12]

7.3 Rezultati intervencije

7.3.1 Perkutana mitralna komisurotomija

Tehnički uspeh i komplikacije su vezani za izbor bolesnika i iskustvo operatera.[164] Dobri početni rezultati koji se definišu kao površina ušća >1.5 cm^2 bez MR>2/4 se postižu u preko 80 % slučajeva. Veće komplikacije uključuju proceduralnu smrtnost 0.5-4 %, hematoperikard 0.5–10 %, embolizam 0.5–5 % i značajnu regurgitaciju 2-10 %. Hitna hirurgija je retko potrebna (<1 %).[165]

Kliničko praćenje potvrđuje uspeh PMC: preživljavanje bez neželjenih događaja nakon 10-20 godina iznosi 30-70 % zavisno od karakteristika bolesnika.[160,166-168] U slučaju kada su početni rezultati nezadovoljavajući, uglavnom je u kratkom roku potrebna operacija.[160,167,168]. Suprotno kada je uspešna PMC dugoročni rezultati su dobri i mogu se predvideti na osnovu preoperativnih anatomskih i kliničkih karakteristika i kvalitetom neposrednih rezultata.[160,167,169] Kada se javi funkcionalno pogoršanje to je kasno nakon intervencije i vezano je uglavnom za restenozu.[170] Uspešna PMC takođe smanjuje embolijski rizik.[163]

7.3.2 Hirurgija

U zemljama u razvoju i dalje se primenjuje zatvorena mitralna komisurotomija, inače je uglavnom zamenjena otvorenom mitralnom komisurotomijom uz kardiopulmonalni bajpas. Rezultati centara sa iskustvom u kojima su uglavnom operisani mlađi bolesnici pokazuju procenat reoperacija 0–7 % za 36–53 % i desetogodišnje preživljavanje 81–90 %.[171,172]

Savremena praksa je uglavnom zamena zalistka kod MS (~95 %). Uglavnom se radi o bolesnicima starije životne dobi i nepovoljnim karakteristikama zalistka da bi se vršila rekonstrukcija.[1,34] Operativni mortalitet kod zamene zalistka kreće se 3–10 % i koreliše sa starošću, funkcionalnom klasom, plućnom hipertenzijom i prisustvom CAD. Dugogodišnje preživljavanje je vezano za starost, funkcionalnu klasu, plućnu hipertenziju, AF, preoperativnu funkciju LV/RV i komplikacije vezane za veštački zalistak.[12]

7.4 Indikacije za intervenciju

Odluku o pravom vremenu kao i vrsti tretmana treba doneti na osnovu kliničkih karakteristika (funkcionalni status, prediktori operativnog rizika kao i rezultati PMC) anatomije zalistka i iskustva operatora. Indikacije za operaciju su kao što je navedeno (tabela 14, slika 4):

- Treba intervenisati samo kod bolesnika sa klinički značajnom MS (površina ušća ≤1.5cm^2).
- Treba intervenisati kod simptomatskih bolesnika.

Kod većine bolesnika sa povoljnom anatomijom zalistka indikovana je PMC. Ipak, kod mladih ljudi sa blagom do umerenom MR iskusni hirurzi češće radije rade otvo-

renu komisurotomiju. Ko bolesnika sa nepovoljnom anatomijom treba detaljno analizirati svaki slučaj imajući u vidu više faktora u predviđanju rezultata PMC.160,170 PMC je idikovana kao inicijalni tretman kod bolesnika sa blagim do umerenim kalcifikacijama ili nepovoljnim subvalvularnim aparatom, koji imaju povoljne kliničke karakteristike, posebno kod mladih bolesnika kod kojih je posebno poželjno odložiti operaciju.[173]

PMC je procedura izbora kada je kontraindikovana operacija ili kao most do operacije kod visokorizičnih kritično bolesnih.

Operacija je indikovana kod bolesnika koji nisu podobni za PMC.

S obzirom da kod PMC rizik postoji, mada je mali, stvarno asimptomatski bolesnici nisu kandidati za procedure, osim u slučajevima kada je povećan rizik od tromboembolizma ili hemodinamske dekompenzacije. Kod njih PMC treba raditi samo ako postoje povoljne karakteristike i to samo iskusni operatori.

Kod asimptomatskih bolesnika sa PMC treba operisati retke bolesnike sa visokim rizikom od komplikacija i bez kontraindikacija za PMC.

Kada je PMC kontraindikovana operacija je jedina opcija (tabela 15). Najznačajnija kontraindikacija za PMC je tromboza LA. Ipak, kada se tromb nalazi u aurikuli leve pretkomore PMC se može izvesti kod bolesnika bez kontraindikacija za operaciju ili kod onih sa hitnom potrebom za intervencijom kod kojih se oralni antikoagulansi mogu bezbedno dati 2–6 meseci sa potvrdom da je tromb nestao ponovljenim TEE. Ukoliko tromb perzistira, indikovana je operacija.

7.5 Farmakološka terapija

Diuretici ili nitrati dugog dejstva prolazno smanjuju dispneu. Beta blokatori ili blokatori kalcijumskih kanala koji regulišu ritam mogu da poprave toleranciju napora. Antikoagulantna terapija sa ciljnim INR-om između 2 i 3 indikovana je kod bolesnika sa permanentnom ili paroksizmalnom AF.[47] Kod bolesnika u sinusnom ritmu antikoagulacija je indikovana kada postoji raniji embolizam ili tromb u levoj pretkomori (preporuka klase I, nivo dokaza C). Takođe je treba razmotriti kada TEE pokaže gust spontani eho kontrast ili uvećanu levu pretkomoru.(M mod diameter >50 mm ili volume leve pretkomore >60ml/m^2) (preporuke klasa IIa, nivo dokaza C).[174]

Aspirin i drugi antitrombocitni lekovi nisu alternativa.

7.6 Serijsko testiranje

Asimptomatske bolesnike sa klinički značajnom MS treba pratiti godišnje klinički i ehokardiografski, a na 2–3 godine u slučaju manje značajne stenoze. Praćenje bolesnika nakon uspešne PMC je kao kod asimptomatskih bolesnika. Kod neuspešne PMC treba bolesnika u što kraćem roku operisati ukoliko ne postoje definitivne kontraindikacije.

7.7 Specijalna populacija bolesnika

Kada se simptomatska restenoza javi posle hirurške komisurotomije ili PMC u većini slučajeva reintervencija zahteva zamenu zalistka. Ponovna PMC se može predložiti kod izabranih bolesnika sa povoljnim karakteristikama ako je dominantni mehanizam komisuralna refuzija i kod inicijalno uspešne PMC kada je do restenoze došlo nakon nekoliko godina. PMC može imati palijativnu ulogu kod bolesnika kod kojih anatomija zalistka nije idealna, ali nisu kandidati za operaciju.[175,176]

O lečenju MS u trudnoći videti sekciju 13.

Kada je hirurgija visoko rizična ili kontraindikovana kod starijih bolesnika, ali je očekivano trajanje života još uvek prihvatljivo, PMC je korisna iako palijativna. Kod bolesnika sa povoljnim anatomskim karakteristikama treba prvo pokušati PMC, a ako su rezultati nezadovoljavajući, operisati. Kod drugih bolesnika operacija je prva opcija.

Kod bolesnika sa značajnom MS kombinovanom sa značajnom aortnom bolešću, operacija je prva opcija.U slučajevima značajne MS sa umerenom bolešću aorte PMC se izvodi da se premosti vreme do operacije oba zalistka.

Kod bolesnika sa značajnom TR, PMC treba pokušati kod bolesnika u sinusnom ritmu, umerenog povećanja leve pretkomore i funkcionalnom TR usled plućne hipertenzije. U drugim slučajevim indikovana je operacija oba zalistka.[177]

Degenerativne kalcifikacije mitralnog zalistka vide se kod starijih bolesnika, posebno sa bubrežnom insuficijencijom, ali retko se razvije u značajnu MS koja zahteva operaciju.

U retkim slučajevima kada poreklo MS nije reumatsko i nema komisuralne fuzije zamena zalistka je jedina opcija.

8. Trikuspidna regurgitacija

Trivijalna TR se često ehokardiografski detektuje kod normalnih ljudi. Patološka TR je češće sekundarna nego primarna. Sekundarna TR je usled dilatacije anulusa i povećanog zatezanja trikuspidnih listića usled povećanog pritiska u RV i/ili opterećenja volumenom. Opterećenje pritiskom je najčešće uzrokovano plućnom hipertenzijom zbog bolesti levog srca ili ređe plućnog srca zbog idiopatske plućne hipertenzije. Opterećenje RV volumenom je uglavnom povezano sa defektom pretkomorskog septuma ili bolešću same desne komore.[12]

8.1 Procena

Simptomi se dominantno javljaju kada postoji bolest zalistka, a čak i značajna TR se može dugo dobro tolerisati. Mada zavise od punjenja, klinički znaci insuficijencije desnog srca su korisni u proceni značajnosti TR.[12]

Opšti principi za invazivnu i neinvazivnu dijagnostiku su kao što je navedeno u preporukama iz *Opštih komentara* (sekcija 3).

Specifičnosti vezane za TR su:

- Ehokardiografija je idealna tehnika za procenu TR. Omogućava sledeće informacije:
  Slična je MR po tome što se po prisustvu ili odsustvu strukturnih abnormalnosti deli na primarnu i sekundarnu. Kod primarne TR etiologija se identifikuje prisustvom specifičnih abnormalnosti kao što su vegetacije kod endokarditisa,[10] zadebljanje listića i retrakcija kod reumatoidne i karcinoidne

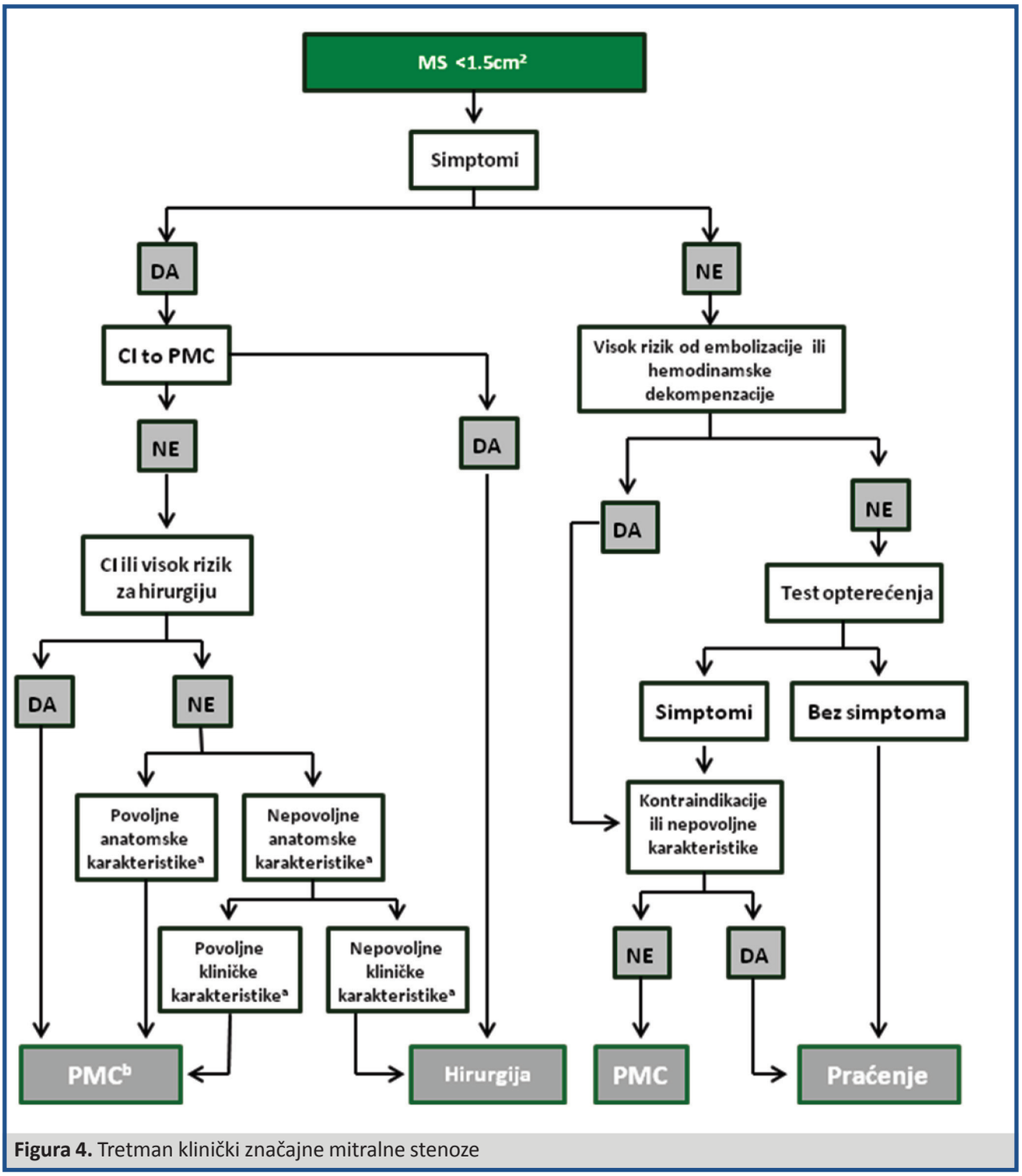


Figura 4. Tretman klinički značajne mitralne stenoze

CI – kontraindikacije; MS – mitralna stenoza; PMC – perkutana mitralna komisurotomija, [a]Videti tabelu 14, [b]Hirušku komisurotomiju treba razmotriti kod bolesnika kod kojih je kontraindikovana perkutana mitralna komisurotomija

bolesti, prolaps listića kod miksomatozne ili traumatske bolesti i displastični trikuspidni zalistak kod kongenitalnih bolesti kao što je Ebstainova anomalija.[11] Stepen dilatacije anulusa takođe se može meriti.[17] Značajna dilatacija trikuspidnog anulusa definisana kao dijastolni dijametar ≥40mm ili >21mm/m² u četvorošupljinskom transtorakalnom preseku.[17,178,180] Kod sekundarne TR koaptaciona distanca >8 mm karakteriše bolesnike sa značajnim zatezanjem (udaljenost između ravni trikuspidnog anulusa i tačke koaptacije u mid-sistoli u apikalnom četvorošupljinskom preseku).[181]

Procenu značajnosti TR i sistolnog pritiska izvesti prema preporukama (tabela 5).[17]

Treba sprovesti procenu dimenzija i funkcije RV bez obzira na ograničenja. Sistolna eskurzija anulusa trikuspidne valvule (TAPSE) (<15 mm), sistolna brzina trikuspidnog anulusa (<11 cm/s), i endsistolna površina RV (>20 cm²) se koriste se za otkrivanje bolesnika sa disfunkcijom RV.[182]

Proceniti prisustvo udruženih lezija (tražiti pažljivo udružene lezije, naročito na levoj strani) i funkciju LV.
- Kada je raspoloživ, CMR predstavlja bolji metod za procenu veličine i funkcije RV.

8.2 Prirodan tok

Ograničeni podaci koji se tiču prirodnog toka primarne TR sugerišu da značajna TR ima lošu prognozu iako se dobro toleriše godinama.[12,183,184] Kao kod levostrane regurgitacije, produžen teret opterećenja volumenom može uzrokovati disfunkciju komore i ireverzibilno oštećenje miokarda. Prolaps trikuspidnog zalistka, (klasično povezan sa značajnom TR) je povezan sa smanjenim preživljavanjem i povećanim rizikom od SI.[184] Sekundarna TR se može smanjiti i nestati kako sa povlačenjem SI. Ipak, TR može perzistirati bez obzira na uspešnu korekciju lezija na levoj strani. Teško je predvideti evoluciju funkcionalne TR nakon hirurškog lečenja bolesti mitralnog zalistka. Plućna hipertenzija, povećan pritisak u RV kao i dimenzije, smanjena funkcija RV, AF, žice pejsmejkera i značajnost deformacije trikuspidnog zalistka (dijametar anulusa, koaptaciona distanca) značajni su faktori rizika za perzistentnu TR ili za pogoršanje TR.[178,180,181]

8.3 Rezultati operacije

Anuloplastika je osnovna operativna tehnika za TR. Bolji rezultati su sa veštačkim prstenom nego sa suturom anulusa, pojava rezidualne TR je 10 % vs 25–30 % na 5 godina.[179,180,185,186] Savremeni stav je da je kod izolovane značajne TR, usled dilatacije prstena, indikovana trikuspidna anuloplastika.[187] Kada je trikuspidni zalistak značajno deformisan, mogu biti korisne komplementarne procedure sa ciljem da se smanji rezidualna postoperativna TR (na primer, uvećanje prednjeg listića).[188] Kod odmaklih formi zatezanja i dilatacije RV treba razmotriti zamenu zalistka. Treba koristiti veću bioprotezu, pre nego mehanički zalistak.[189] Dodavanje rekonstrukcije trikuspidnog zalistka operaciji levog srca ne povećava operativni rizik. Desetogodišnje preživljavanje je od 30 do 50 %. Prediktori su preoperativna funkcionalna klasa, disfunkcija RV i LV i komplikacije kod veštačkog zalistka.[185–189] Kada postoje žice pejsmejkera i TR tehniku treba prilagoditi stanju bolesnika i iskustvu hirurga. Reoperacija na trikuspidnom zalistku u slučajevima perzistentne TR nakon operacije mitralnog zalistka nosi najveći rizik, uglavnom zbog kliničkog stanja bolesnika (s obzirom na starost i broj prethodnih intervencija na srcu) i može imati loše dugoročne rezultate vezane za prisustvo ireverzibilnog oštećenja desne komore pre reoperacije ili disfunkciju miokarda ili zalistaka LV.

8.4 Indikacije za operaciju

Ostaje otvoreno pitanje trenutka hirurške intervencije, uglavnom zato što su dostupni podaci malobrojni i heterogeni. (tabela 16). Kao opšti princip treba usvojiti da je bolja rekonstrukcija nego zamena zalistka i da treba operisati dovoljno rano da se izbegne ireverzibilno oštećenje RV.

Odluka da se operiše trikuspidni zalistak se donosi istovremeno sa odlukom da se vrši korekcija levostranih zalistaka. Operacija TR je indikovana kod bolesnika sa značajnom TR. Kada postoji značajno dilatiran anulus (≥40 mm), treba operisati i bolesnike sa umerenom primarnom TR, kao i bolesnike sa blagom ili umerenom sekundarnom TR.[178,180]

Izolovana operacija trikuspidnog zalistka je preporučena kod simptomatskih bolesnika sa značajnom primarnom TR. Mada ti bolesnici imaju dobar odgovor na terapiju diureticima, odlaganje operacije često ima za rezultat ireverzibilno oštećenje desne komore, oštećenje organa i loše rezultate kasnije operacije. Mada su granične vrednosti slabo definisane (slično kao kod MR), asimptomatske bolesnike sa značajnom primarnom TR treba pažljivo pratiti da se otkrije progresivno uvećanje desne komore, kao i razvoj rane disfunkcije RV što zahteva hitnu hirurišku intervenciju.

Kada postoji povratna značajna TR nakon operacije levostranog zalistka, treba razmotriti izolovanu operaci-

Tabela 16. Indikacije za operaciju trikuspidnog zalistka

	Klasa[a]	Nivo[b]
Operacija je indikovana kod simptomatskih bolesnika sa značajnom TS[c].	I	C
Operacija je indikovana kod bolesnika sa značajnom TS koji idu na operaciju zalistka na levoj strani.[d]	I	C
Operacija je indikovana kod bolesnika sa značajnom primarnom ili sekundarnom TR koji idu na operaciju zalistka na levoj strani.	I	C
Operacija je indikovana kod simptomatskih bolesnika sa značajnom izolovanom primarnom TR bez značajne disfunkcije desne komore.	I	C
Operaciju treba razmotriti kod bolesnika sa umerenom primarnom TR koji idu na operaciju zalistka na levoj strani.	IIa	C
Operaciju treba razmotriti kod bolesnika sa blagom ili umerenom sekundarnom TR sa dilatiranim anulusom (≥40mm ili >21mm/m²) koji idu na operaciju zalistka na levoj strani.	IIa	C
Operaciju treba razmotriti kod asimptomatskih ili blago simptomatskih bolesnika sa značajnom izolovanom primarnom TR i progresivnom dilatacijom desne komore ili pogoršanjem funkcije desne komore.	IIa	C
Nakon operacije zalistka na levoj strani, operaciju treba razmotriti kod bolesnika sa značajnom TR koji su simptomatski ili imaju progresivnu dilataciju/disfunkciju RV u odsustvu disfunkcije valvule levog srca, teže disfunkcije desne ili leve komore i teže vaskularne plućne bolesti.	IIa	C

PMC – perkutana mitralna komisurotomija; TR – trikuspidna regurgitacija; TS – trikuspidna stenoza, [a]Klasa preporuka, [b]Nivo dokaza, [c]Perkutana balon valvuloplastika se može pokušati ako je izolovana TS, [d]Perkutana balon valvuloplastika se može pokušati ako je moguće izvesti PMC na mitralnom zalistku.

ju na trikuspidnom zalistku koji su simptomatski ili imaju progresivno uvećanje i disfunkciju RV, *u odsustvu* disfunkcije levostranih zalistaka, značajne disfunkcije LV ili značajne bolesti plućne vaskulature.

Za lečenje Ebstainove anomalije videti referencu 11 (Baumgartner et al).

8.5 Farmakološka terapija

Diuretici smanjuju kongestiju.

9. Trikuspidna stenoza

Trikuspidna stenoza (TS), koja je uglavnom reumatskog porekla, retko se viđa u razvijenim zemljama, mada se nalazi u zemljama u razvoju.[3,12] Otkrivanje zahteva pažljivu procenu, mada je skoro uvek vezano za oboljenj levostranih zalistaka koje dominira kliničkom slikom.

9.1 Procena

Klinički znaci su često maskirani pridruženim bolestima zalistaka, posebno MS.[12,190] Ehokardiografija pruža najkorisnije informacije. TS se često previdi i zahteva pažljivu procenu. Metod poluvremena pada pritiska je manje koristan u proceni TS, nego MS, a jednačina kontinuiteta nije podobna zbog uglavnom prisutne TR. Planimetrija ušća je moguća samo pomoću TEE. Nema generalno prihvaćenog gradiranja TS. Srednji gradijent ≥5 mmHg je indikativan za značajnu TS kod bolesnika u sinusnom ritmu i sa normalnom frekvencom.[15] Ehokardiografskim pregledom treba utvrditi postoji li komisuralna fuzija, kakva je anatomija zalistka i subvalvularnog aparata, što je značajno u proceni mogućnosti rekonstrukcije, kao i stepena prateće TR.

9.2 Hirurgija

Nedostatak savitljivog tkiva listića je glavni ograničavajući faktor za rekonstrukciju. Mada se o tome i dalje raspravlja u upotrebi su češće biološke proteze u odnosu na mehaničke, zbog visokog rizika od tromboze mehaničkih i duge trajnosti bioloških kada su na tikuspidnoj poziciji.[189–191]

9.3 Perkutane intervencije

Perkutana balon dilatacija trikuspidnog zalistka se retko izvodi samostalno ili uz PMC, ali često uzrokuje značajnu regurgitaciju. Nedostaju podaci o proceni dugoročnih rezultata.[192]

9.4 Indikacije za intervenciju

Intervencija na trikuspidnom zalistku se izvodi istovremeno sa intervencijom na drugim zaliscima kod simptomatskih bolesnika uprkos farmakološkoj terapiji. Konzervativna hirurgija ili zamena zalistka, zavisno od anatomije zalistka i iskustva hirurga u rekonstrukciji zalistka, bolji je metod nego balon komisurotomija koju treba razmotriti samo u retkim slučajevima izolovane TS (tabela 16).

9.5 Farmakološka terapija

Diuretici su korisni u prisustvu SI, ali ograničeno efikasni.

10. Kombinovana i bolest više zalistaka

Značajna stenoza i regurgitacija se često mogu naći kod istog bolesnika. Bolest više zalistaka se nalazi primarno kod reumatske bolesti srca i ređe kod degenerativnih bolesti zalistaka. Nema dovoljno podataka o mešovitim i bolestima više zalistaka da bi se govorilo o preporukama zasnovanim na dokazima.[190]

Opšti principi za lečenje su:

- Kada je dominantna stenoza ili regurgitacija lečenje je prema preporukama koje se odnose na dominantnu bolest zalistka. Kada je uravnotežena težina stenoze i regurgitacije indikacije za intervenciju su prema simptomima i objektivnim posledicama, pre nego pokazateljima značajnosti stenoze ili regurgitacije.
- Osim odvojene procene svakog zalistka pojedinačno, potrebno je uzeti u obzir interakciju odvojenih zalistaka. Na primer, značajna MR može dovesti do potcenjivanja AS, s obzirom da smanjeni udarni volumen kod MR smanjuje protok kroz aortni zalistak i time gradijent nad njim. To ističe potrebu da se kombinuju različita merenja, uključujući i procenu površine ušća, ako je moguće koristeći metod koji nije zavistan od uslova punjenja kao što je planimetrija.
- Indikacije za intervenciju se zasnivaju na globalnoj proceni posledica različitih lezija zalistaka, tj. simptoma ili postojanja disfunkcije i dilatacije leve komore. Intervenciju treba planirati kod multiplih lezija koje su svaka za sebe neznačajne, ali su povezane sa simptomima ili vode oštećenju LV.
- Kada se planira intervencija na više zalistaka, treba uzeti o obzir povećan rizik kod kombinovanih procedura.
- Pri izboru operativne tehnike treba uzeti u obzir prisustvo druge bolesti zalistka. Mada je rekonstrukcija zalistka idealno rešenje, kada treba implantirati jedan veštački zalistak smanjuje se motiv da se drugi rekonstruiše.

Lečenjem specifičnih bolesti zalistaka bave se odvojena poglavlja.

11. Veštački zalisci

Bolesnici kod kojih je ranije učinjena operacije zalistka čine 28 % svih bolesnika sa bolešću zalistaka u evropskom istraživanju bolesti srca (Euro Heart Survey).[1] Izbor optimalnog veštačkog zalistka, kao i dalji tretman bolesnika sa veštačkim zaliscima suštinski su za smanjenje komplikacija.

11.1 Izbor veštačkog zalistka

Nema savršene zamene za zalistak. Svaka zamena podrazumeva određene kompromise i svaka predstavlja uvođenje u novu bolest, bilo da je zalistak mehanički (sa jednim diskom ili dva poludiska) ili biološki. Biološki uključuju homograftove, plućne autograftove i svinjske, goveđe perikardijalne i ili konjske bioproteze.

Tabela 17. Izbor aortne/mitralne proteze. U korist mehaničkih proteza

	Klasa[a]	Nivo[b]
Želja dobro informisanog bolesnika i odsustvo kontraindikacija za dugotrajnu antikoagulantnu terapiju[c].	I	C
Bolesnici u riziku za ubrzanu degeneraciju valvule[c].	I	C
Bolesnici koji su već na antikoagulantnoj terapiji zbog drugih mehaničkih proteza.	I	C
Bolesnici <60 godina za protezu na aortnoj poziciji i <65 godina za protezu na mitralnoj poziciji[e].	IIa	C
Bolesnici sa dugim očekivanim trajanjem života[f] i oni kod kojih bi ponovna operacija bila pod visokim rizikom.	IIa	C
Bolesnici koji su već na antikoagulantnoj terapiji zbog visokog rizika od tromboembolija[g].	IIb	C

Odluka se zasniva na integraciji više faktora, [a]Klasa preporuka, [b]Nivo dokaza, [c]Povećan rizik od krvarenja zbog komorbiditeta, nedovoljne saradnje, podneblja i profesije, [d]Starost <40 godina, hiperparatireoidizam, [e]Kod bolesnika starosti 60–65 godina za protezu na aortnoj poziciji i 65-70 za protezu na mitralnoj poziciji oba zalistka su prihvatljiva i izbor zahteva analizu drugih faktora osim starosti, [f]Trajanje života se procenjuje >10 godina prema starosti, polu, komorbiditetima i prosečnom trajanju života na određenom području, [g]Faktori rizika za tromboembolizam su fibrilacija pretkomora, raniji tromboembolizam, hiperkoagulabilno stanje, značajna disfunkcija leve komore

Tabela 18. Izbor aortne/mitralne proteze. U korist bioproteza

	Klasa[a]	Nivo[b]
Želja dobro informisanog pacijenta.	I	C
Kada postoji mala šansa za kvalitetnu antikoagulaciju (problemi sa saradnjom, neraspoloživost), kontra-indikacije zbog visokog rizika od krvarenja (ranije veće krvarenje; komorbiditeti, nevoljnost, životni stil, profesija).	I	C
Re-operacija zbog tromboze veštačke valvule kod pacijenta sa dokazano lošom antikoagulantnom kontrolom.	I	C
Bolesnici kod kojih bi eventualna ponovna hirurgija bila sa niskim rizikom.	IIa	C
Mlade žene koje planiraju trudnoću.	IIa	C
Bolesnici starosti >65 godina za protezu na aortnoj poziciji ili >70 godina na mitralnoj poziciji ili oni čije je pretpostavljano trajanje života[c] manje nego prosečno trajanje bioproteze[d].	IIa	C

Odluka se zasniva na integraciji više faktora, [a]Klasa preporuka, [c]Trajanje života se procenjuje prema starosti, polu, komorbiditetima i prosečnom trajanju života na određenom području, [d] Kod bolesnika starosti 60–65 godina za protezu na aortnoj poziciji i 65–70 za protezu na mitralnoj poziciji oba zalistka su prihvatljiva i izbor zahteva analizu drugih faktora osim starosti

Ksenografovi se mogu dalje podeliti na stentovane i one bez stenta. Oni bez stenta mogu imati hemodinamski bolje karakteristike, ali nije pokazano da su izdržljiviji.[193] Bioproteze koje se ne ušivaju su tehnologija budućnosti, sa mogućnošću lakog plasiranja i veće efektivne površine ušća.

U upotrebi su dve vrste proteza koje se implantiraju preko katetera. Napravljene su od tkiva perikarda koje je umetnuto u metalni stent koji se širi balonom ili stent od nitinola koji se širi sam.

Svi mehanički zalisci zahtevaju doživotnu antikoagulaciju. Sa biološkim zaliscima nije potrebna antikoagulacija osim iz drugih indikacija, ali su kratkog veka trajanja.

Homografovi i plućni autografovi se koriste na aortnoj poziciji kod odraslih, mada čine ukupno manje od 1% ZAZ i kratkog su veka trajanja. Analizom nije pokazano da su homografovi trajniji od perikardnih bioproteza, a bioproteze bez stenta su se pokazale trajnijim od homografova.[194,195] Prosečno vreme do reoperacije zbog propadanja homografa zavisi od starosti bolesnika i varira od prosečno 11 godina kod 20-godišnjaka do prosečno 25 godina kod 65-godišnjaka.[194,195] Tehnička ograničenja, mala raspoloživost i povećana složenost reoperacije ograničavaju upotrebu homografova.[196] Iako je i dalje pod znakom pitanja, osnovna indikacija za homografove je akutni infektivni endokarditis sa perivalvularnom lezijom.[10,197]

Prebacivanje plućnog autografta na aortnu poziciju (Rosova procedura) omogućava odličnu hemodinamiku, ali zahteva izuzetnu stručnost i ima nekoliko mana: rizik od rane stenoze plućnog grafta, rizik od povratka aortne regurgitacije aortnog korena i rizik od reumatskog procesa.[198] Mada se Rosova operacija ponekad radi kod odraslih (profesionalni sportisti ili žene koje planiraju trudnoću), osnovna populacija su deca jer zalistak i aortni anulus nastavljaju da rastu sa detetom, što nije slučaj kod homografova. Potencijalne kandidate za Rosovu operaciju treba uputiti u centre sa iskustvom.[11]

U praksi izbor je uglavnom između mehaničke i bioproteze sa stentom.

Raznovrsnost bolesti zalistaka i različitost ishoda čine teškim dizajn prospektivnih randomizovanih studija. Dva randomizovana istraživanja koja su poredila starije modele mehaničkih i bioloških zalistaka nisu našli značajnu razliku u stepenu tromboze zalistka i tromboembolizmu. Dugoročno preživljavanje je bilo vrlo slično.[199,200] Najnovije istraživanje koje je poredilo mehaničke i biološke proteze obuhvatilo je 310 bolesnika starosti 55–70 godina.[210] Nije bilo razlike u preživljavanju, tromboembolizmu i stopi krvarenja, ali je kod bioproteza pokazan veći stepen propadanja zalistka i broj reoperacija. Meta analiza opservacionih serija nije pokazala razliku u preživljavanju uzimajući u obzir karakteristike bolesnika. Modeli mikrosimulacije mogu pomoći u individualnom izboru za svakog bolesnika omogućavajući procenu preživljavanja bez negativnih događaja vezanih za zalistak uzimajući u obzir starost bolesnika i tip proteze.[202]

Izbor valvule ne određuju samo njene hemodinamske karakteristike već procena rizika od krvarenja usled antikoagulacije i tromboembolizma kod mehaničkih zalistaka, u poređenju sa propadanjem zalistka kod bioproteze, kao i bolesnikove želje i navike.[46,203,205]

Rizik od tromboembolizma i krvarenja je određen uglavnom ciljnim INR-om, kvalitetom kontrole antikoagulacije, udruženom upotrebom aspirina i faktorima rizika vezanim za samog bolesnika. Rizik vezan za propadanje zalistka opada sa starošću i veći je na mitralnoj nego na aortnoj poziciji. Rizik od reoperacije je malo veći nego kod prve operacije.[203]

Izbor proteze treba da je individualan, prilagođen svakom bolesniku. Kardiolog, hirurg i sam bolesnik donose odluku zajedno uzimajući u obzir faktore prikazane u tabelama 17 i 18. Kod bolesnika starosti 60–65 godina, koji treba da prime aortni zalistak, i oni starosti 65–70 godina za mitralni zalistak obe opcije su prihvatljive i izbor zahteva analizu dodatnih faktora. Treba uzeti u obzir sledeće karakteristike:

- Bioproteze uzeti u obzir kod bolesnika čije je očekivano trajanje života kraće nego pretpostavljena trajnost bioproteze, naročito ako će zbog komorbiditeta biti potrebne i druge hirurške procedure, kao i kada postoji rizik od krvarenja. Mada je propadanje zalistka ubrzano kod hronične insuficijencije bubrega, kratko očekivano trajanje života i povećan rizik od komplikacija zbog mehaničkog zalistka ipak daju prednost biološkom zalistku u ovoj situaciji.[206]
- Kod žena koje žele da zatrudne visok rizik od tromboembolijskih komplikacija sa mehaničkom protezom tokom trudnoće i mali rizik elektivne reoperacije su motivi za bioprotezu, bez obzira na njeno rapidno propadanje u ovoj starosnoj grupi.[207]
- Moraju se uzeti u obzir i kvalitet života i želje informisanog bolesnika. Nelagodnost u vezi sa antikoagulantnom terapijom se smanjuje samoangažovanjem bolesnika oko njene regulacije. Mada bolesnici sa bioprotezom time izbegavaju antikoagulaciju suočavaju se sa pogoršavanjem funkcionalnog statusa zbog propadanja zalistka kao i potrebom da se reoperišu ukoliko žive dovoljno dugo.
- Tokom srednjeročnog praćenja kod nekih bolesnika sa biološkim zalistkom može nastati druga indikacija za antikoagulantnu terapiju (AF, moždani udar, periferna arterijska bolest i drugo)

Uticaj neslaganja veštački zalistak-bolesnik ukazuje na potrebu da se ugrade proteze sa najvećom efektivnom površinom ušća, mada podaci dobijeni in vitro i geometrijska površina ušća nisu dovoljno pouzdani.[208] Ako je očekivani odnos veštački zalistak-bolesnik <0.65 cm^2/m^2 BSA, razmotriti povećanje anulusa kako bi se postavila veća proteza.[209]

11.2 Vođenje bolesnika nakon zamene zalistka

Tromboembolizam i krvarenje vezano za antikoagulaciju su komplikacije kod bolesnika sa veštačkim zaliscima.[12] Profilaksa endokarsitisa i lečenje endokarditisa su opisani u posebnim ESC preporukama.[10]

11.2.1 Osnovna procena i modaliteti praćenja

Kompletnu procenu treba napraviti 6–12 meseci nakon operacije. To uključuje kliničku procenu, Rtg grudnog koša, EKG, TTE i analize krvi. Najznačajnije je za procenu eventualnih promena u šumu i zvuku veštačkog zalistka, kao i komorskoj funkciji, transvalvularnom gradijentu i odsustvu paravalvularne regurgiracije. Ovu postoperativnu posetu treba iskoristiti za poboljšanje edukacije bolesnika o profilaksi infektivnog endokarditisa i antikoagulantnoj terapiji i istaći da se u slučaju pojave simptoma odmah jave lekaru.

Sve bolesnike kojima je zamenjen zalistak treba redovno klinički pratiti, godišnje, a u slučaju pojave simptoma češće. TTE treba raditi u slučaju pojave simptoma nakon ugradnje zalistka ili ako se sumnja da postoje komplikacije. Godišnji ehokardiografski pregled se preporučuje posle pete godine nakon ugradnje bioproteze i ranije kod mlađih bolesnika. Transvalvularni gradijent se najbolje interpretira u poređenju sa bazalnim vrednostima, bolje nego sa teorijskim za datu protezu. TEE treba raditi u slučaju da je loš kvalitet TTE i u slučaju kada se sumnja na disfunkciju proteze ili endokarditis.[210]

Fluoroskopiju i MSCT treba raditi ako se sumnja na tromb ili panus.[211]

11.2.2 Vođenje antikoagulacije

11.2.2.1 Opšti principi

Pravilno vođenje antikoagulacije se odnosi na kontrolu faktora rizika kao i prepisivanje antitrombotskih lekova.[203,212,213]

Indikacije za antitrombotsku terapiju nakon zamene ili rekonstrukcije zalistka su prikazane u tabeli 19.

Raniji stav je bio da se nakon postavljanja aortne bioproteze tri meseca koristi antikoagulantna terapija, sada se sve više koristi niska doza aspirina.[214,215]

Zamena antagonista vitamina K direktnim oralnim inhibitorima faktora IIa ili Xa još nije odobrena za bolesnike sa mehaničkim protezama.

Kada je indikovana postoperativna antikoagulantna terapija, oralnu antikoagulantnu terapiju treba početi prvog postoperativnog dana. Intravenski nefrakcionisani heparin uz ciljnu vrednost aktiviranog parcijalnog tromboplastinskog vremena (aPTT) 1.5–2.0 kontrolne vrednosti omogućava brzu antikoagulaciju do porasta INR. Niskomolekularni heparin (LMWH) nudi stabilnu i efektivnu antikoagulaciju i korišćen je u manjim opservacionim serijama.[216] Upotreba nije zvanično odobrena. Ograničavajući faktori za ranu postoperativnu primenu nakon ugradnje veštačkog zalistka su nedostatak randomizovanih kliničkih istraživanja, pitanja oko farmakokinetike kod gojaznih bolesnika i ciljne anti Xa aktivnosti, kontraindikacija kod značajne insuficijencije bubrega i nemogućnost da se neutrališe. Ako se koristi LMWH, treba pratiti anti Xa aktivnost.

Prvi postoperativni mesec je period visokog rizika za tromboembolizam i antikoagulacija ne sme da bude niža nego što je preporučena, naročito kod bolesnika sa veštačkim mitralnim zalistkom.[217,218] Kao dodatak u tom periodu antikoagulacija je podložnija varijacijama i treba je češće pratiti.

Uprkos nedostatku dokaza kombinacija niske doze aspirina i tienopiridina se koristi rano nakon TAVI i perkutane rekonstrukcije „edge to edge", nastavlja se samo aspirinom ili tienopiridinom. Kod bolesnika sa AF indikovana je kombinacija antagonista vitamina K i aspirina ili tienopiridina, ali treba proceniti rizik od krvarenja.

Tabela 19. Indikacije za antitrombotsku terapiju nakon operacije zalistka

	Klasa[a]	Nivo[b]	Ref[c]
Indikovana je doživotna antikoagulantna terapija kod svih bolesnika sa mehaničkim zaliscima.	I	B	
Preporučuje se doživotna antikoagulantna terapija kod bolesnika sa bioprotezama koji imaju druge indikacije za antikoagulantnu terapiju[d].	I	C	
Kod bolesnika sa udruženom aterosklerotskom bolešću preporučuje se dodavanje niske doze aspirina.	IIa	C	
Dodavanje niske doze aspirina preporučuje se kod bolesnika sa mehaničkom protezom uprkos adekvatnom INR.	IIa	C	
Oralna antikoagulacija prva tri meseca nakon implantacije mitralne i trikuspidne bioproteze.	IIa	C	
Oralna antikoagulacija prva tri meseca nakon rekonstrukcije mitralnog zalistka.	IIa	C	
Niska doza aspirina prva tri meseca nakon implantacije aortne bioproteze.	IIa	C	
Oralna antikoagulacija prva tri meseca nakon implantacije aortne bioproteze.	IIb	C	

[a]Klasa preporuka, [b]Nivo dokaza, [c]Reference podržavaju klasu I (A+B) i IIa+IIb(A+B) preporuka, [d]Atrijalna fibrilacija, venski tromboemolizam, hiperkoagulabilno stanje i sa manjim nivoom dokaza značajno oštećena funkcija leve komore (ejekciona frakcija <35 %)

11.2.2.2 Ciljni INR

U izboru optimalnog ciljnog INR-a treba uzeti u obzir individualne faktore rizika i trombogenost proteze, koja je određena prema stepenu prijavljenih tromboza za dati zalistak u odnosu na specifične vrednosti INR-a (tabela 20).[203,219] Trenutno raspoloživa randomizovana istraživanja koja porede različite vrednosti INR-a ne mogu se koristiti za određivanje INR-a u svim situacijama i različite metodologije čine ih nepodobnim za metaanalize.[220–222]

Pri određivanju optimalnog INRa obratiti pažnju na sledeće:

- Trombogenost proteze ne zavisi samo od dizajna (dvolisne, sa diskom, itd.) ili datuma pojave na tržištu.
- Za mnoge proteze koje su od nedavno u upotrebi ne postoji dovoljno podataka o stepenu tromboze pri različitim vrednostima INR-a. Dok se ne sakupi dovoljno podataka treba ih smatrati srednje trombogenim.
- Ciljni INR treba smanjiti u slučaju da se jave rekurentna krvarenja ili povećati u slučaju tromboembolizma.

Tabela 20. Ciljni INR za mehaničke proteze

Trombogenost proteze[a]	Faktori rizika vezani za bolesnika[b]	
	Bez faktora rizika	≥1 Faktor rizika
Niska	2.5	3.0
Srednja	3.0	3.5
Visoka	3.5	4.0

[a]Trombogenost proteze: Niska – Carbomedics (aorna pozicija), Medtronic Hall, St Jude Medical, ON-X; Srednja – druge dvolisne valvule; Visoka – Lillehei-Kaster, Omniscience, Starr-Edwards, Bjork-Shiley i drugi zalisci sa diskom, [b]Faktori rizika vezani za bolesnika: zamena mitralnog ili trikuspidnog zalistka; raniji tromboembolizam; atrijalna fibrilacija; mitralna stenoza bilo kog stepena; ejekciona frakcija leve komore <35%;

Preporuka je da se koristi srednja vrednost INR-a, radije nego opseg, s obzirom da su vrednosti na krajevima opsega manje bezbedne i efektivne nego vrednosti na sredini.

Visoka varijabilnost INR-a je snažan nezavisan prediktor smanjenog preživljavanja nakon zamene zalistka. Samostalno podešavanje antikoagulacije dokazano smanjuje varijabilnost INR-a i kliničkih događaja, ali zahteva obučenost. Praćenje INR-a na klinici je za bolesnike sa nestabilnim INR-om ili komplikacijama.

11.2.2.3 Postupak kod predoziranja antagonista vitamina K i krvarenja

Rizik od većeg krvarenja značajno raste kada je INR iznad 4.5 i eksponencijalno raste kod INR iznad 6. INR≥6 zahteva brzu reverziju antikoagulacije zbog rizika od krvarenja. U odsustvu krvarenja postupak zavisi od ciljnog INR-a, stvarnog INR-a i poluvremena života antagonista vitamina K koji je korišćen. Može se obustaviti antikoagulantna terapija, ili pustiti da INR postupno pada, ili dati oralni vitamin K u dozi 1 ili 2 mg.[223] Ako je INR>10, treba dati veće doze vitamina K (5 mg). Oralna primena je bolja od intravenske koja nosi rizik od anafilakse.[223]

Trenutna reverzija antikoagulacije je potrebna samo kod značajnog krvarenja nepodobnog za lokalnu kontrolu, koje ugrožava život ili funkciju vitalnih organa (npr. intrakranijalno krvarenje), uzrokuje hemodinamsku nestabilnost ili zahteva hitnu hiruršku proceduru ili transfuziju. Intravenski protrombinski kompleks ima kratak poluživot i treba ga kombinovati sa oralnim vitaminom K bez obzira na INR.[223] Intravenski protrombinski kompleks ima prednost u odnosu na svežu zamrznutu plazmu. Upotreba rekombinovanog aktiviranog faktora VII se ne može preporučiti zbog nedovoljno podataka. Nema podataka koji bi ukazivali da prolazni rizik od tromboembolija nadmašuje korist od prestanka krvarenja kod bolesnika sa mehaničkim zaliscima. Optimalno vreme za nastavak antikoagulacije zavisi od lokacije krvarenja, evolucije i intervencija koje su bile potrebne da se ono zaustavi i/ili da se tretira njegov uzrok. Treba paziti na krverenje koije se javlja u terapijskom opsegu INR i naći i lečiti njegov uzrok.

11.2.2.4 Kombinacija oralnih antikoagulanasa i atitrombocitnih lekova

Kod donošenja odluke da se bolesniku sa veštačkim zalistkom antitrombocitni lek doda antikoagulantnom važno je odvojiti posebne koristi za koronarnu i vaskularnu bolest i one specifične za mehaničke zalistke. Istraživanja koja su pokazala korist antitrombocitnih lekova kod vaskularnih bolesti i kod bolesnika sa veštačkim zaliscima ne treba koristiti kao dokaz da će bolesnici sa mehanič-

kim zaliscima, a bez vaskularnih bolesti, takođe imati korist.[224] Kada se dodaju antikoagulantnim antitrombocitni lekovi povećavaju rizik od većih krvarenja.[225,226] Njih dakle ne treba prepisivati svim bolesnicima sa veštačkim zaliscima, nego samo kod određenih indikacija vodeći računa o riziku od krvarenja. Koriste se manje doze (npr. aspirin≤100 mg/dan).

Indikacije za dodavanje antitrombocitne terapije su prikazane u tabeli 19. Treba je uvoditi uz uvažavanje rizika od krvarenja i nakon optimizacije antikoagulantne terapije.

Dodavanje aspirina i blokatora $P2Y_{12}$ je potrebno nakon intrakoronarnog stentiranja, ali povećava rizik od krvarenja. Kod bolesnika sa mehaničkim zaliscima treba ugrađivati metalne stentove neobložene lekom, kako bi se skratila upotreba trostruke antitrombotske terapije na mesec dana.[20] Duža upotreba (3–6 meseci) je potrebna u određenim slučajevima nakon akutnog koronarnog sindroma.[47] Tokom tog perioda potrebno je pažljivo pratiti INR i izbeći preteranu antikoagulaciju.[20]

Konačno nije indikovano prepisivati antitrombocitnu terapiju bolesnicima sa ugrađenom bioprotezom duže od tri meseca ukoliko je jedina indikacija prisustvo bioproteze.

11.2.2.5 Prekidanje antikoagulantne terapije

Antikoagulacija tokom nesrčanih operacija zahteva pažljivo vođenje, bazirano na proceni rizika.[203,227] Osim faktora vezanih za protezu i samog bolesnika (tabela 20), operacije zbog maligne bolesti ili infektivnog procesa nose poseban rizik zbog hiperkoagulabilnosti u tim stanjima.

Preporuka je da se za manje hirurške procedure ne prekida antikoagulacija (kao što su vađenje zuba, operacija katarakte), kao i one procedure kod kojih se krvarenje može lako kontrolisati (preporuka klase I, nivo dokaza C). INR treba meriti na dan procedure i treba koristiti odgovarajuće tehnike hemostaze.[228,229]

Velike hirurške procedure zahtevaju INR<1.5. Kod bolesnika sa mehaničkim protezama treba obustaviti oralnu antikoagulantnu terapiju pre procedure i preporučeno je premošćavanje pomoću heparina (preporuka klase I, nivo dokaza C).[227-229] Nefreakcionisani heparin je jedini odobren kod bolesnika sa veštačkim zaliscima (preporuka klase IIa, nivo dokaza C). Supkutani LMWH može poslužiti kao alternativa (preporuka klase IIa, nivo dokaza C). Ipak uprkos njihovoj širokoj upotrebi i pozitivnim rezultatima opservacionih studija[230,231] LMWH nije odobren kod bolesnika sa mehaničkim zaliscima zbog toga što nedostaju kontrolisane komparativne studije sa UFH. Kada se koristi LMWH, treba ga promeniti dva puta dnevno u terapijskoj dozi, prilgođeno telesnoj težini i, ako je moguće, uz praćenje anti-Xa aktivnosti sa ciljnim vrednostima 0.5–1.0 U/ml.[227] LMWH je kontraindikovan u slučaju značajne insuficijencije bubrega. Poslednju dozu LMWH treba ordinirati >12 h pre procedure, dok UFH treba obustaviti 4h pre operacije. Efektivnu antikoagulaciju treba uspostaviti što ranije nakon hirurške procedure prema riziku od krvarenja i održavati je dok se INR ne vrati u terapijski opseg.[227]

Ako je potrebno, posle pažljive procene koristi i rizika, kombinovanu aspirinsku terapiju treba prekinuti 1 nedelju pre nesrčane procedure.

Oralnu antikoagulaciju treba nastaviti u modifikovanoj dozi kod većine bolesnika kod kojih se radi kateterizacija srca, posebno kod radijalnog pristupa. Kod bolesnika kod kojih je potrebna transseptalna kateterizacija, direktna punktura LV ili drenaža perikarda, treba obustaviti oralnu antikoagulaciju i premostiti heparinom kao što je gore opisano.[203]

Kod bolesnika kod kojih je na kontroli primećeno da imaju supterapeutski INR potrebno je premošćavanje sa NFH illi bolje LMWH u ambulantnim uslovima dok se ne postigne ciljni INR.

11.2.3 Postupak kod tromboze zalistka

Na opstruktivnu trombozu zalistka treba posumnjati kod svakog bolesnika sa bilo kojim tipom zalistka koji se javi sa skoro nastalom dispneom ili embolijskim događajem. Verovatnoća je veća kada postoji podatak o skorašnjoj neadekvatnoj antikoagulaciji ili razlozima za povećanu koagulabilnost (dehidratacija, infekcija i sl.). Dijagnozu treba potvrditi pomoću TTE i/ili TEE ili fluoroskopijom.[210,232]

Lečenje tromboze zalistka je visokorizično bez obzira na način. Operacija je visokorizična zbog toga što je u pitanju reintervencija i radi se u uslovima hitnosti. Sa druge strane fibrinoliza nosi rizik od krvarenja, sistemske embolizacije i povratnih tromboza.[233]

Analizu koristi i rizika treba prilagoditi karakteristikama bolesnika i lokalnim sredstvima.

Hitna zamena zalistka se preporučuje kod kritičnih bolesnika sa opstruktivnom trombozom bez značajnih komorbiditeta (preporuka klase I, nivo dokaza C: slika 5) Ukoliko je trombogenost proteze značajan faktor, treba je zameniti manje trombogenom protezom.

Fibrinolizu raditi u sledećim slučajevima:

- kritični bolesnici koji imaju male šanse da prežive operaciju zbog komorbiditeta ili značajno loše funkcije srca pre razvoja tromboze;
- situacije u kojima hirurgija nije trenutno dostupna ili se bolesnik ne može transportovati;
- tromboza trikuspidnog ili plućnog zalistka zbog velike uspešnosti i malog rizika od sistemske embolizacije.

Kod hemodinamske nestabilnosti koristi se kratak protokol, koristeći ili rekombinovani tkivni activator plazminogena ili 10 mg bolus + 90 mg u 90 min. sa UFH ili streptokinaza 1 500 000 U u 60 min bez UFH. Duže trajanje infuzije je za stabilnije bolesnike.[234]

Fibrinoliza je manje uspešna kod tromboze mitralne proteze, hronične tromboze, kod prisustva panusa, koji se teško razlikuje od tromba. [210,233]

Neopstruktivna tromboza se dijagnostikuje pomoću TEE koji se radi nakon embolijskog događaja ili sistematski praćenjem proteze na mitralnoj poziciji. Postupak zavisi od pojave tromboemboliskog događaja i veličine tromba (slika 6). Obavezno je pažljivo praćenje pomoću TEE. Kod malih tromba (<10 mm) prognoza je povoljna. Dobar odgovor sa postepenim smanjenjem tromba otklanja potrebu za operacijom. Opearcija je indikovana kod velikih (≥10mm) neopstruktivnih tromba komplikovanih embolizmom (preporuka klase IIa, nivo dokaza C) ili kojira i perzistira uprkos optimalnoj antikoagulaciji.[217] Fi-

brinolizu treba razmotriti ukoliko je operacija visokorizična. Ipak treba je upotrebiti samo kada je apsolutno neophodno zbog rizika od krvarenja i tromboembolizma.

11.2.4 Postupak kod tromboembolizma

Poreklo tromboembolizma nakon operacije zalistaka je multifaktorijalno.[203] Mada tromboembolijski događaji često potiču od proteze, mnogi imaju druge uzroke koji se javljaju u opštoj populaciji i u osnovi su šloga i tranzitornih ishemijskih ataka.

Stoga je nužno pažljivo ispitivanje svake tromboze. (uključujući srčana i nesrčana snimanja: slika 6) pre nego se odluči da se podigne ciljni INR ili doda antitrombocitni lek. Prevencija daljih tromboembolijskih događaja uključuje:

- otklanjanje i lečenje faktora rizika kao što su AF, hipertenzija, hiperholesterolemija, pušenje, infekcija i protrombotični poremećaji krvi;
- optimizacija antikoagulantne kontrole, ako je moguće bolesnik sam sebe kontroliše. To treba obaviti u konsultaciji sa neurologom u slučaju skorašnjeg moždanog udara;
- treba dodati nisku dozu aspirina (≤100 mg/dan) posle pažljive analize korist, rizik, izbegavajući preteranu antikoagualciju.

11.2.5 Postupak kod hemolize i paravalvularne regurgitacije

Testovi na hemolizu treba da su deo rutinskog praćenja nakon ugradnje zalistka. Haptoglobin je suviše osetljiv i laktat dehidrogenaza je, mada nespecifična, bolji pokazatelj značajnosti hemolize. Dijagnoze hemolitičke anemije zahteva TEE da se proceni paravalvularna regurgitacija ako TTE nije dovoljno informativan. Reoperacija se preporučuje ukoliko je paravalvularna regurgitacija vezana za endokarditis ili ako uzrokuje hemolizu koja zahteva ponavljane transfuzije krvi ili daje značajne simptome (preporuka klase I, nivo dokaza C). Farmakološka terapija uključujući nadoknadu gvožđa, beta blokatore i eritropoetin je indikovana kod bolesnika sa značajnom anemijom i paravalvularnom regurgitacijom koja nije vezana za endokarditis, kada postoje kontraindikacije za operaciju ili kada bolesnici odbijaju reoperaciju.[235] Transkatetersko zatvaranje je izvodljivo, ali iskustva su ograničena i nema dokaza da je postojano efikasno.[236] Može se razmotriti za odabrane bolesnike kod kojih je reintervencija procenjena kao visokorizična ili je kontraindikovana.

11.2.6 Postupak kod gubitka funkcije biološkog zalistka

Nakon prvih 5 godina od ugradnje, i ranije kod mladih bolesnika potrebno je raditi ehokardiografiju jednom godišnje da bi se utvrdili rani znaci degeneracije zalistka, zadebljanja listića, kalcifikacije, smanjenje efektivne površine ušća, i/ili regurgitacija. Auskultatorne i ehokardiografske znake treba pratiti i porediti sa prethodnim nalazima istog bolesnika. Reoperacija je indikovana kod simptomatskog bolesnika sa značajnim porastom transvalvularnog gradijenta ili značajnom regurgitacijom (preporuka klase I, nivo dokaza C). Reoperciju treba razmotriti kod svakog asimptomatskog bolesnika sa znacima značajne disfunkcije zalistka ukoliko nisu visokorizični (preporuka klase IIa, nivo dokaza C). Profilaktička zamena proteze koja je stara >10 godina, bez propadanja zalistka, može se razmotriti u toku operacije drugog zalistka ili koronarnih arterija (preporuka klase IIa, nivo dokaza C).

Pri donošenju odluke da se reoperiše treba uzeti u obzir hitnost situacije i rizik od reoperacije. To ističe značaj pažljivog praćenja radi pravovremene intervencije.[237]

Kod stenoze levostranih bioproteza treba izbegavati perkutane balon intervencije.

Kod gubitka funkcije bioproteze izvodljiva se pokazala intervencija transkateterske implantacije „zalistak u zalistak".[238,239] Iskustva su ograničena tako da se ne može smatrati kao validna alternativa operaciji, osim kod inoperabilnih visokorizičnih bolesnika prema proceni kardiohirurškog tima.

11.2.7 Srčana insuficijencija

Kada se SI javi nakon operacije zalistka uzrok je moguće vezan za zalistak, neuspela rekonstrukcija, disfunkcija LV ili progresija bolesti drugog zalistka.Komplikacije koje nisu vezane za zalistak su koronarna bolest, hipertenzija, aritmije. Postupak kod bolesnika sa SI je isti kao što je opisano u odgovarajućim preporukama.[13]

12. Postupak tokom nesrčanih operacija

Kardiovaskularni morbiditet i mortalitet je povećan kod bolesnika sa valvularnim bolestima koji idu na nesrčane operacije. Pravilno perioperativno vođenje bolesnika sa valvularnim bolestima manje je zasnovano na dokazima nego vođenje bolesnika sa ishemijskom bolešću srca.[227]

12.1 Preoperativna procena

Kliničku procenu uključuje potraga za simptomima, aritmijama i prisustvom šuma – što opravdava potrebu za ehokardiografijom, posebno kod starijih.

Kardiovaskularni rizik se takođe rangira prema tipu nesrčane operacije i klasifikuje prema riziku od srčanih komplikacija.[227]

Svaki bolesnik zahteva individualni pristup i odluku zajednički donose kardiolog, anesteziolog, hirurg (kardiohirurg i hirurg koji će operisati) i bolesnik sa porodicom.

12.2 Specifične bolesti zalistaka

12.2.1 Aortna stenoza

Kod bolesnika sa značajnom aortnom stenozom hitna nesrčana operacija se izvodi uz pažljivo hemodinamsko praćenje.

Bolesnici sa značajnom AS kod kojih je potrebna elektivna nesrčana operacija postupak zavisi uglavnom od postojanja simptoma i tipa operacije (slika 7).[227,240,241]

Kod simptomatskih bolesnika ZAZ treba planirati pre nesrčanih operacija. Ako postoji visok rizik za operaciju zalistka treba revidirati potrebu da se izvodi nesrčana operacija, pre nego da se planira balon valvuloplastika ili TAVI.

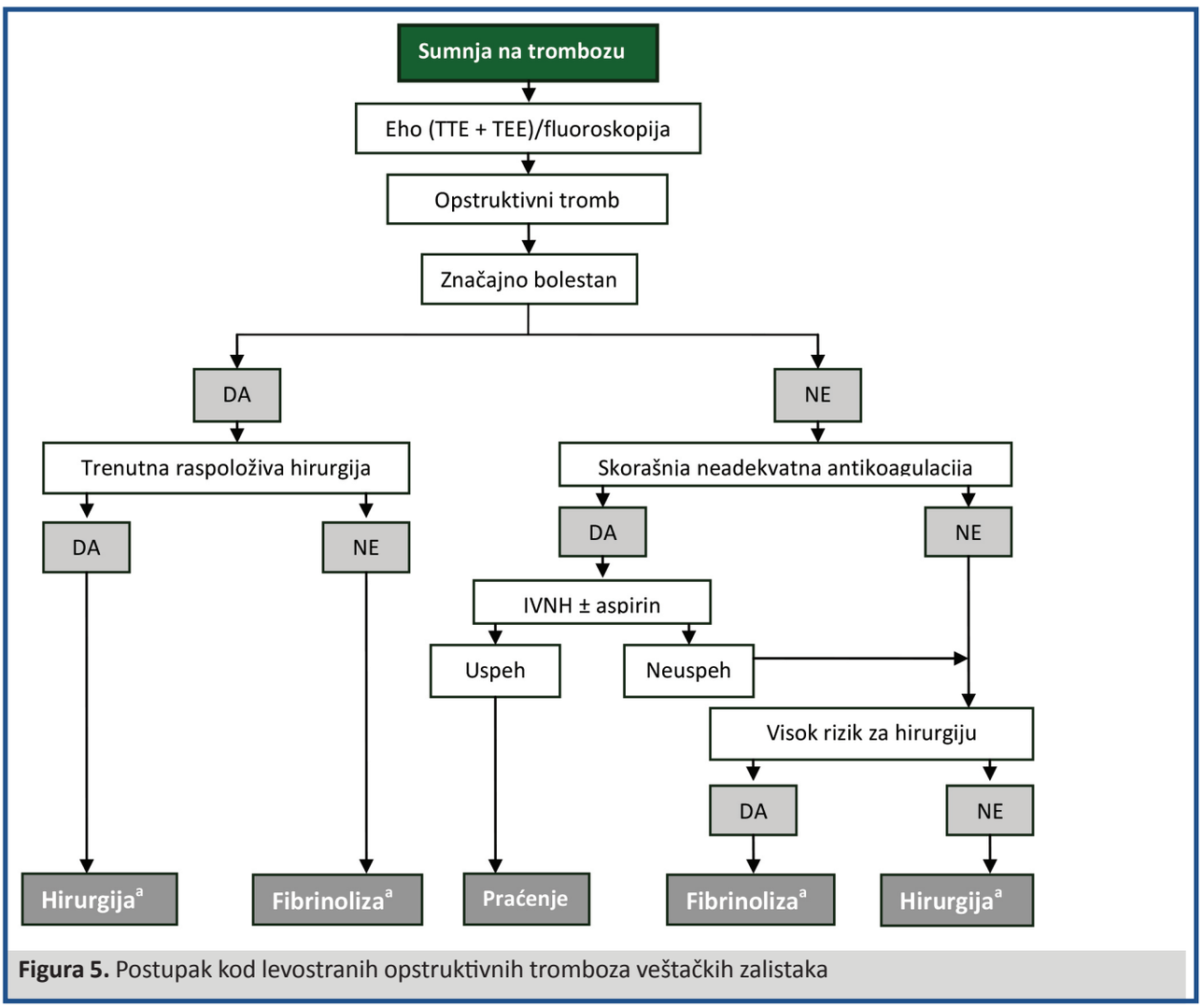


Figura 5. Postupak kod levostranih opstruktivnih tromboza veštačkih zalistaka

Legenda: TTE – transtoraksna ehokardiografija, TEE – trasezofagusna ehokardiografija

Kod asimptomatskih bolesnika sa značajnom AS, može se izvesti nesrčana operacija niskog ili umerenog rizika.[240] Ako se radi o nesrčanoj operaciji visokog rizika, postojanje značajne AS, značajnih kalcifikacija zalistka ili nenormalnog testa opterećenja su znaci su da je potrebno prvo uraditi ZAZ.

Kod asimptomatskih bolesnika koji su visokorizični za ZAZ, nesrčanu operaciju, ukoliko je obavezna, treba izvesti pod strogim hemodinamskim nadzorom.

Kada je operaciju zalistka potrebno izvesti pre nesrčane operacije, bolje je ugraditi bioprotezu kako bi se izbegli problemi sa antikoagulacijom.

12.2.2 Mitralna stenoza

Kod asimptomatskoh bolesnika sa značajnom mitralnom stenozom i sistolnim pritiskom u plućnoj arteriji <50 mmHg može se bezbedno izvesti nesrčana operacija.

Kod simptomatskih bolesnika ili kod bolesnika sa sistolnim plućnim pritiskom >50 mmHg treba korigovati mitralnu manu, ako je moguće PMC, ako je nesrčana operacija visokorizična. Ukoliko je potrebna zamena zalistka, odluku treba doneti pažljivo.

12.2.3 Aortna i mitralna regurgitacija

Kod bolesnika sa značajnom aortnom i mitralnom regurgitacijom i očuvanom funkcijom LV nesrčana operacija se može bezbedno izvesti. Prisustvo simptoma ili disfunkcije LV vodi u razmatranje operacije zalistka, ali to je retko potrebno. Ako je disfunkcija LV značajna (EF<30 %), nesrčanu operaciju treba izvesti tek nakon optimizacije farmakološke terapije za SI i to samo ako je neophodno.

12.2.4 Veštački zalisci

Osnovni problem je prilagođavanje antikoagulacije što je detaljno opisano u poglavlju *Prekidanje antikoagulantne terapije* (sekcija 11.2.2.5.)

12.3 Perioperativno praćenje

Perioperativno praćenje je usmereno na kontrolu srčanog ritma (posebno kod MS), izbegavanje volumnog opterećenja i dehidratacije i hipotenzije (posebno kod AS) i optimizaciju antikoagulacije.[240]

Kod bolesnika sa umerenom do značajnom aortnom stenozom i mitralnom stenozom, mogu se, radi održanja sinusnog ritma, profilaktički koristiti amiodaron i

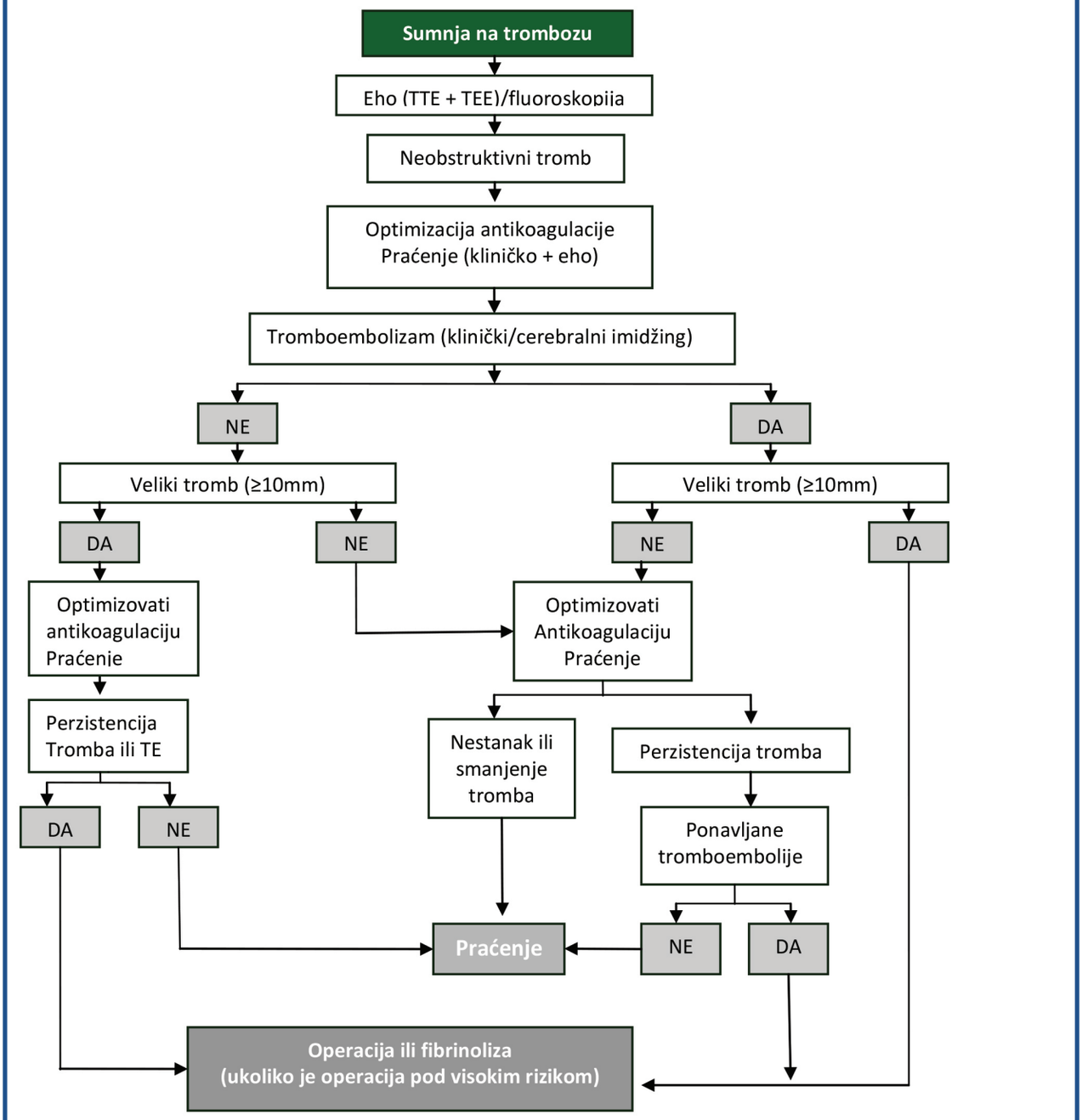


Figura 6. Postupak kod levostranih neopstruktivnih tromboza veštačkih zalistaka

Legenda:TTE -transtoraksna ehokardiografija,TEE - trasezofagusna ehokardiografija,TE-tromboembolizam

beta blokatori.[241] Upotreba beta blokatora i statina treba da je usklađena sa rizikom od ishemijske bolesti srca prema preporukama.

Razumno je bolesnike sa značajnom valvularnom manom nakon operacije pratiti u intenzivnoj nezi.

13. Postupak tokom trudnoće

Vođenje bolesnica sa valvularnom bolesti srca tokom trudnoće je detaljno opisano u odgovarajućim preporukama.[207] Ukratko, vođenje trudnoće i planiranje porođaja je saradnja akušera, kardiologa i bolesnice i njene porodice. Bolest zalistka bi trebalo otkriti i lečiti pre trudnoće. U određenim okolnostima trudnoća nije preporučljiva.

13.1 Bolest nativnih zalistaka

MS se u trudnoći loše toleriše kada je površina ušća <1.5 cm^2 čak i kod prethodno asimptomatskih bolesnica. Simptomatsku MS treba lečiti mirovanjem i beta blokatorima, kao i diureticima. U slučaju uporne dispnee i plućne arterijske hipertenzije uprkos terapiji, treba razmotriti PMC u centru sa iskustvom preko 20 nedelje gestacije. U određenim slučajevima indikovana je antikoagulacija.[207]

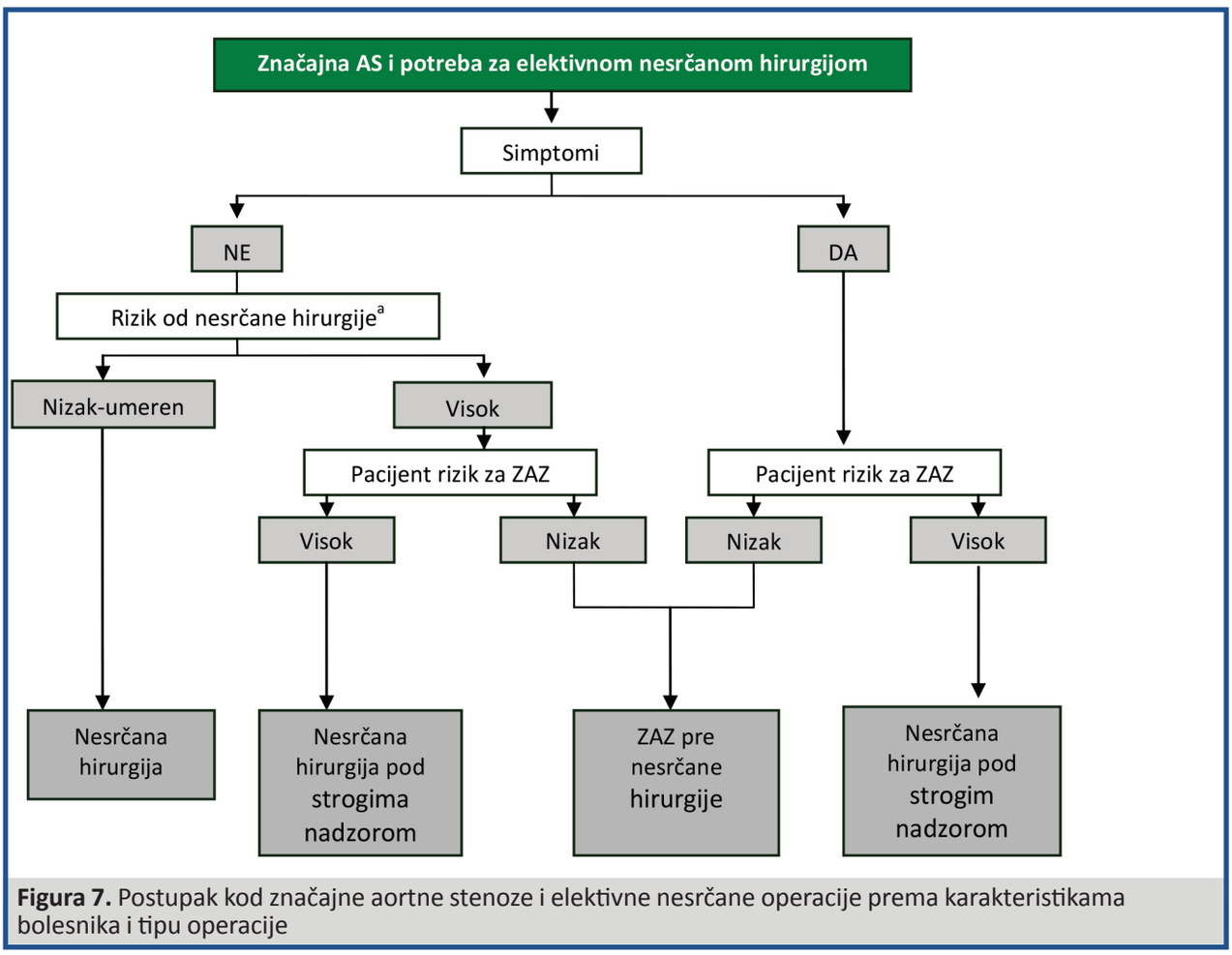


Figura 7. Postupak kod značajne aortne stenoze i elektivne nesrčane operacije prema karakteristikama bolesnika i tipu operacije

AS – aortna stenoza; ZAZ – zamena aortnog zalistka; BAV – balon aortna valvuloplastika; TAVI – transkateterska implantacija aortne valvule [a]Klasifikacija u tri grupe prema riziku od srčanih komplikacija (30-dnevna smrt i miokardni infarkt) za nesrčanu hirurgiju (227) (visoki rizik>5%; umereni rizik 1–5 %; mali rizik<1 %), [b] nesrčana hirurgija će biti izvedena samo ako je neophodno. Izbor izmedju aortne balon valvuloplastike i transkateterske implantacije aortne valvule zavisiće od očekivanog životnog veka pacijenta.

Komplikacije značajne AS javljaju se uglavnom kod bolesnica koje su bile asimptomatske pre trudnoće. Rizik od SI je nizak kada je srednji aortni gradijent <50 mmHg.

Hronične MR i AR se dobro podnose, čak i u slučaju kada su značajne, dok je očuvana funkcija LV. Operacija pod kardiopulmonalnim bajpasom je vezana sa smrtnošću fetusa 20–30% i indikovana samo u retkim slučajevima kada je ugrožen život majke.

13.2 Veštački zalisci

Kod prisustva veštačkog zalistka mortalitet majke je 1-4 %. U slučaju da dođe do trudnoće ove bolesnice treba uputiti u rizike i ograničenja usled antikoagulantne terapije. Tokom prvog trimestra treba izabrati između antagonista vitamina K, LMWH i UFH pažljivo odmerivši rizik po majku i fetus. Antagonisti vitamina K su indikovani tokom drugog i trećeg trimestra, do 36 nedelje, kada ih treba zameniti heparinom.[207]

Literatura

1. Lung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, Tornos P, Vanoverschelde JL, Vermeer F, Boersma E, Ravaud P, Vahanian A. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on Valvular Heart Disease. Eur Heart J 2003;24:1231–1243.
2. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. Lancet 2006;368:1005–1011.
3. Carapetis JR, Steer AC, Mulholland EK,Weber M. The global burden of group A streptococcal diseases. Lancet Infect Dis 2005;5:685–694.
4. Iung B, Cachier A, Baron G, Messika-Zeitoun D, Delahaye F, Tornos P, Gohlke-Bärwolf C, Boersma E, Ravaud P, Vahanian A. Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery? Eur Heart J 2005;26:2714–2720.
5. Mirabel M, Lung B, Baron G, Messika-Zeitoun D, De´taint D, Vanoverschelde JL, Butchart EG, Ravaud P, Vahanian A. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? Eur Heart J 2007;28:1358–1365.
6. Van Geldorp MWA, van Gameren M, Kappetein AP, Arabkhani B, de Groot-de Laat LE, Takkenberg JJ, Bogers AJ. Therapeutic decisions for patients with symptomatic severe aortic stenosis: room for improvement? Eur J Cardiothorac Surg 2009;35:953–957.
7. Bach DS, Awais M, Gurm HS, Kohnstamn S. Failure of guidelines adherence for intervention in patients with severe mitral regurgitation. J Am Coll Cardiol 2009; 54:860–865.

8. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, Hall R, Iung B, Kasprzak J, Nataf P, Tornos P, Torracca L, Wenink A, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Angelini A, Antunes M, Garcia Fernandez MA, Gohlke-Baerwolf CG, McMurray J, Otto C, Pierard L, Pomar JL, Prendergast B, Rosenhek R, Sousa Uva M, Tamargo J. Guidelines on the management of valvular heart disease: the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J 2007;28: 230–268.
9. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS. 2008 focused update incorporated into the ACC/ AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anaesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol 2008;52:e1–e142.
10. Habib G, Hoen B, Tornos P, Thuny F, Prendergast B, Vilacosta I, Moreillon P, Antunes M, Thilen U, Lekakis J, Lengyel M, Müller L, Naber CK, Nihoyannopoulos P, Moritz A, Zamorano JL, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, McGregor K, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P. Document Reviewers, Vahanian A, Aguilar R, Bongiorni MG, Borger M, Butchart E, Danchin N, Delahaye F, Erbel R, Franzen D, Gould K, Hall R, Hassager C, Kjeldsen K, McManus R, Miro´ JM, Mokracek A, Rosenhek R, San Román Calvar JA, Seferovic P, Selton-Suty C, Sousa Uva M, Trinchero R, van Camp G. Guidelines on the prevention, diagnosis, and treatment of infective endocarditis (new version 2009): the Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and by the International Society of Chemotherapy (ISC) for Infection and Cancer. Eur Heart J 2009;30:2369–2413.
11. Baumgartner H, Bonhoeffer P, De Groot NMS, de Haan F, Deanfield JE, Galie N, Gatzoulis MA, Gohlke-Baerwolf C, Kaemmerer H, Kilner P, Meijboom F, Mulder BJM, Oechslin E, Oliver JM, Serraf A, Szatmari A, Thaulow E, Vouhe PR, Walma E, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas P, Widimsky P, McDonagh T, Swan L, Andreotti F, Beghetti M, Borggrefe M, Bozio A, Brecker S, Budts W, Hess J, Hirsch R, Jondeau G, Kokkonen J, Kozelj M, Kucukoglu S, Laan M, Lionis C, Metreveli I, Moons P, Pieper PG, Pilossoff V, Popelova J, Price S, Roos-Hesselink J, Sousa Uva M, Tornos P, Trigo Trindade P, Ukkonen H, Walker H, Webb GD, Westby J; Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC). ESC Guidelines for the management of grown-up congenital heart disease (new version 2010). Eur Heart J 2010;31: 2915–2957.
12. Vahanian A, Iung B, Pierard L, Dion R, Pepper J. Valvular heart disease. In: Camm AJ, Lüscher TF, Serruys PW, ed. The ESC Textbook of Cardiovascular Medicine, 2nd Edition. Malden/ Oxford/Victoria: Blackwell Publishing Ltd; 2009:625–670 13. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bo¨hm M, Dickstein K, Falk V, Filippatos G, Fonseca C, Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitter J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A; ESC Committee for Practice Guidelines (CPG), Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S; Document Reviewers, McDonagh T, Sechtem U, Bonet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Iung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur Heart J 2012;33: 1787–1847.
14. Popescu BA, Andrade MJ, Badano LP, Fox KF, Flachskampf FA, Lancellotti P, Varga A, Sicari R, Evangelista A, Nihoyannopoulos P, Zamorano JL on behalf of the European Association of Echocardiography, Document Reviewers, Derumeaux G, Kasprzak JD, Roelandt JRTC. Recommendations for training, competence, and quality improvement in echocardiography. Eur J Echocardiogr 2009;10:893–905.
15. Baumgartner H, Hung J, Bermejo J, Chambers JB, Evangelista A, Griffin BP, Iung B, Otto CM, Pellikka PA, Quiñones M. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. Eur J Echocardiogr 2009;10:1–25.
16. Lancellotti P, Tribouilloy C, Hagendorff A, Moura L, Popescu BA, Agricola E, Monin JL, Pierard LA, Badano L, Zamorano JL. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease). Eur J Echocardiogr 2010; 11:223–244.
17. Lancellotti P, Moura L, Pierard LA, Agricola E, Popescu BA, Tribouilloy C, Hagendorff A, Monin JL, Badano L, Zamorano JL. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2: mitral and tricuspid regurgitation (native valve disease). Eur J Echocardiogr 2010;11:307–332.
18. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, Solomon SD, Louie EK, Schiller NB. Guidelines for the Echocardiographic Assessment of the Right Heart in Adults: A Report from the American Society of Echocardiography endorsed by the European Association of Echocardiography and the Canadian Society of Echocardiography J Am Soc Echocardiogr 2010; 23:685–713.
19. Lang RM, Badano LP, Tsang W, Adams DH, Agricola E, Buck T, Faletra FF, Franke A, Hung J, Perez de Isla L, Kamp O, Kasprzak JD, Lancellotti P, Marwick TH, McCulloch ML, Monaghan MJ, Nihoyannopoulos P, Pandian NG, Pellikka PA, Pepi M, Roberson DA, Shernan SA, Shirali GS, Sugeng L, Ten Cate FJ, Vannan MA, Zamorano JL, Zoghbi WA. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. Eur Heart J Cardiovasc Imag 2012;13:1–46.
20. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, Garg S, Huber K, James S, Knuuti J, Lopez-Sendon J, Marco J, Menicanti L, Ostojic M, Piepoli MF, Pirlet C, Pomar JL, Reifart N, Ribichini FL, Schalij MJ, Sergeant P, Serruys PW, Silber S, Sousa Uva M, Taggart D, Vahanian A, Auricchio A, Bax J, Ceconi C, Dean V, Filippatos G, Funck-Brentano C, Hobbs R, Kearney P, McDonagh T, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Vardas PE, Widimsky P, Alfieri O, Dunning J, Elia S, Kappetein P, Lockowandt U, Sarris G, Vouhe P, von Segesser L, Agewall S, Aladashvili A, Alexopoulos D, Antunes MJ, Atalar E, Brutel de la Riviere A, Doganov A, Eha J, Fajadet J, Ferreira R, Garot J, Halcox J, Hasin Y, Janssens S, Kervinen K, Laufer G, Legrand V, Nashef SA, Neumann FJ, Niemela K, Nihoyannopoulos P, Noc M, Piek JJ, Pirk J, Rozenman Y, Sabate M, Starc R, Thielmann M, Wheatley DJ, Windecker S, Zembala M. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2010;31:2501–2555.
21. Picano E, Pibarot P, Lancellotti P, Monin JL, Bonow RO. The emerging role of exercise testing and stress echocardiography in valvular heart disease. J Am Coll Cardiol 2009;54:2251–2260.
22. Monin JL, Quéré JP, Monchi M, Petit H, Baleynaud S, Chauvel C, Pop C, Ohlmann P, Lelguen C, Dehant P, Tribouilloy C, Guéret P. Low-gradient aortic stenosis, operative risk stratification and predictors for long-term outcome: a multicenter study using dobutamine stress hemodynamics. Circulation 2003;108:319–324.
23. Cawley PJ, Maki JH, Otto CM. Cardiovascular magnetic resonance imaging for valvular heart disease. Circulation 2009;119:468–478.
24. Cueff C, Serfaty JM, Cimadevilla C, Laissy JP, Himbert D, Tubach F, Duval X, Iung B, Enriquez-Sarano M, Vahanian A, Messika-Zeito-

un D. Measurement of aortic valve calcification using multislice-multi-slice computed tomography: correlation with haemodynamic severity of aortic stenosis and clinical implication for patients with low ejection fraction. Heart 2011;97:721–726.
25. Ketelsen D, Fishman EK, Claussen CD, Vogel-Claussen J. Computed tomography evaluation of cardiac valves: a review. Radiol Clin North Am 2010;48: 783–797.
26. Kaleschke G, Seifarth H, Kerckhoff G, Reinecke H, Baumgartner H. Imaging decision-making for transfemoral or transapical approach of transcatheter aortic valve implantation. EuroIntervention 2010;6(Suppl G):G20–27.
27. Messika-Zeitoun D, Serfaty JM, Brochet E, Ducrocq G, Lepage L, Detaint D, Hyafil F, Himbert D, Pasi N, Laissy JP, Iung B, Vahanian A. Multimodal assessment of the aortic annulus diameter: implications for transcatheter aortic valve implantation. J Am Coll Cardiol 2010;55:186–194.
28. Plein S, Schulz-Menger J, Almeida A, Mahrholdt H, Rademakers F, Pennell D, Nagel E, Schwitter J, Lombard M. Training and accreditation in cardiovascular magnetic resonance in Europe: a position statement of the working group on cardiovascular magnetic resonance of the European Society of Cardiology. Eur Heart J, 2011;32:793–798.
29. Steadman CD, Ray S, Ng LL, McCann GP. Natriuretic peptides in common valvular heart disease. J Am Coll Cardiol 2010;55:2034–2048.
30. Gerber MA, Baltimore RS, Eaton CB, Gewitz M, Rowley AH, Shulman ST, Taubert KA. Prevention of rheumatic fever and diagnosis and treatment of acute Streptococcal pharyngitis: a scientific statement from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young, the Interdisciplinary Council on Functional Genomics and Translational Biology, and the Interdisciplinary Council on Quality of Care and Outcomes Research: endorsed by the American Academy of Pediatrics. Circulation 2009;119:1541–1551.
31. Rosenhek R, Iung B, Tornos P, Antunes MJ, Prendergast BD, Otto CM, Kappetein AP, Stepinska J, Kaden JJ, Naber CK, Acartürk E, Gohlke-Bärwolf C. ESC Working Group on Valvular Heart Disease Position Paper: assessing the risk of interventions in patients with valvular heart disease. Eur Heart J 2012; 33:822–828.
32. The European Association for Cardio-Thoracic Surgery. Fourth EACTS adult cardiac surgical database report 2010. Henley-on-Thames, UK Dendrite Clinical Systems Ltd; ISBN 9781-9039-682-60.
33. The Society of Thoracic Surgeons. Adult cardiac surgery database, executive summary, 10 years STS report. http://www.sts.org/sites/default/files/documents/ pdf/ndb2010/1stHarvestExecutiveSummary%5B1%5D.pdf.
34. Bridgewater B, Keogh B, Kinsman R, Walton P. The Society for Cardiothoracic Surgery in Great Britain & Ireland, 6th national adult cardiac surgical database report; demonstrating quality, 2008. Henley-on-Thames, UK: Dendrite Clinical Systems Ltd; ISBN 1-903968-23-2, published July 2009.
35. Gummert JF, Funkat A, Beckmann A, Schiller W, Hekmat K, Ernst M, Beyersdorf F. Cardiac surgery in Germany during 2009. A report on behalf of the German Society for Thoracic and Cardiovascular Surgery. Thorac Cardiovasc Surg 2010;58:379–386.
36. Rankin JS, Hammill BG, Ferguson TB Jr., Glower DD, O'Brien SM, DeLong ER, Peterson ED, Edwards FH. Determinants of operative mortality in valvular heart surgery. J Thorac Cardiovasc Surg 2006;131:547–557.
37. Ambler G, Omar RZ, Royston P, Kinsman R, Keogh BE, Taylor KM. Generic, simple risk stratification model for heart valve surgery. Circulation 2005;112: 224–231. 38. van Gameren M, Kappetein AP, Steyerberg EW, Venema AC, Berenschot EA, Hannan EL, Bogers AJ, Takkenberg JJ. Do we need separate risk stratification models for hospital mortality after heart valve surgery? Ann Thorac Surg 2008; 85:921–930. 39. Parolari A, Pesce LL, Trezzi M, Cavallotti L, Kassem S, Loardi C, Pacini D, Tremoli E, Alamanni F. EuroSCORE performance in valve surgery: a meta-analysis. Ann Thorac Surg 2010;89:787–793, 793.e1–e2.
40. Dewey TM, Brown D, Ryan WH, Herbert MA, Prince SL, Mack MJ. Reliability of risk algorithms in predicting early and late operative outcomes in high-risk patients undergoing aortic valve replacement. J Thorac Cardiovasc Surg 2008; 135:180–187.
41. Osswald BR, Gegouskov V, Badowski-Zyla D, Tochtermann U, Thomas G, Hagl S, Blackstone EH. Overestimation of aortic valve replacement risk by Euro- SCORE: implications for percutaneous valve replacement. Eur Heart J 2009;30: 74–80.
42. Lee DH, Buth KJ, Martin BJ, Yip AM, Hirsch GM. Frail patients are at increased risk for mortality and prolonged institutional care after cardiac surgery. Circulation 2010;121:973–978.
43. Lee SJ, Lindquist K, Segal MR, Covinsky KE. Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 2006;295:801–808.
44. Gammie JS, O'Brien SM, Griffith BP, Ferguson TB, Peterson ED. Influence of hospital procedural volume on care process and mortality for patients undergoing elective surgery for mitral regurgitation. Circulation 2007;115:881–887.
45. Adams DH, Rosenhek R, Falk V. Degenerative mitral valve regurgitation: best practice revolution. Eur Heart J 2010;31:1958–1966.
46. Montori VM, Ting HH. Sharing decision making about cardiac surgery: improving the quality of the decision to undergo or forego surgery. Circ Cardiovasc Qual Outcomes 2009;2:519–521.
47. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, Van Gelder IC, Al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, De Caterina R, De Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, Le Heuzey JY, Ponikowski P, Rutten FH. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J 2010;31:2369–2429.
48. Enriquez-Sarano M, Tajik AJ. Clinical practice: aortic regurgitation. N Engl J Med 2004;351:1539–1546.
49. Pierard LA, Moonen M, Lancellotti P. Valvular regurgitation. In: Zamorano JL, Bax J, Rademakers F, Knuuti J, eds. The ESC textbook of cardiovascular imaging. Springer, 2010:150–159.
50. Detaint D, Messika-Zeitoun D, Maalouf J, Tribouilloy C, Mahoney DW, Tajik J, Enriquez-Sarano M. Quantitative echocardiographic determinants of clinical outcome in asymptomatic patients with aortic regurgitation. JACC. Cardiovascular imaging 2008;1:1–11.
51. Evangelista A, Flachskampf FA, Erbel R, Antonini-Canterin F, Vlachopoulos Ch, Rocchi G, Sicari R, Nihoyannopoulos P, Zamorano J. Echocardiography in aortic diseases: EAE recommendations for clinical practice. Eur J Echocardiogr 2010;11;645–658.
52. La Canna G, Maisano F, De Michele L, Grimaldi A, Grassi F, Capritti E, De Bonis M, Alfieri O. Determinants of the degree of functional aortic regurgitation in patients with anatomically normal aortic valve and ascending thoracic aorta aneurysm. Transoesophageal Doppler echocardiography study. Heart 2009;95: 130–136.
53. le Polain de Waroux JB, Pouleur AC, Goffinet C, Vancraeynest D, Van Dyck M, Robert A, Gerber BL, Pasquet A, El Khoury G, Vanoverschelde JLJ. Functional anatomy of aortic regurgitation: accuracy, prediction of surgical repairability, and outcome implications of tranesophageal echocardiography. Circulation 2007;116 (11 suppl):I264–269.
54. Sambola A, Tornos P, Ferreira-Gonzalez I, Evangelista A. Prognostic value of preoperative indexed end-systolic left ventricle diameter in the outcome after surgery in patients with chronic aortic regurgitation. Am Heart J 2008;155: 1114–1120.
55. Marciniak A, Sutherland GR, Marciniak M, Claus P, Bijnens B, Jahangiri M. Myocardial deformation abnormalities in patients with aortic regurgitation: a strain rate imaging study. Eur J Echocardiogr 2009;10:112–119.
56. Goffinet C, Kersten V, Pouleur AC, Le Polain de Waroux JB, Vancraeynest D, Pasquet A, Vanoverschelde JL, Gelber BL. Comprehensive assessment of the severity and mechanism of aortic regurgitation using multidetector CT and MR. Eur Radiol 2010;20:326–336.
57. Bonow RO, Lakatos E, Maron BJ, Epstein SE. Serial long-term assessment of the natural history of asymptomatic patients with chronic aortic regurgitation and normal left ventricular systolic function. Circulation 1991;84:1625–1635.
58. Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany CJ, Bailey KR, Seward JB. Optimizing timing of surgical correction in patients with severe aortic regurgitation: role of symptoms. J Am Coll Cardiol 1997;30:746–752.
59. Dujardin KS, Enriquez-Sarano M, Schaff HV, Bailey KR, Seward JB, Tajik AJ. Mortality and morbidity of aortic regurgitation in clinical practice. A long-term follow-up study. Circulation 1999;99:1851–1857.

60. Jondeau G, Detaint D, Tubach F, Arnoult F, Milleron O, Raoux F, Delorme G, Mimoun L, Krapf L, Hamroun D, Beroud C, Roy C, Vahanian A, Boileau C. Aortic event rate in the Marfan population: a cohort study. Circulation 2012; 125:226–232.
61. Judge DP, Dietz HC. Marfan's syndrome. Lancet 2005;366:1965–1976.
62. Keane MG, Wiegers SE, Plappert T, Pochettino A, Bavaria JE, Sutton MG. Bicuspid aortic valves are associated with aortic dilatation out of proportion to coexistent valvular lesions. Circulation 2000;102(19 Suppl 3):pIII-35–39.
63. Davies RR, Kaple RK, Mandapati D, Gallo A, Botta DM, Elefteriades JA, Coady MA. Natural history of ascending aortic aneurysms in the setting of an unreplaced bicuspid aortic valve. Ann Thorac Surg 2007;83:1338–1344.
64. Tzemos N, Therrien J, Yip J, Thanassoulis G, Tremblay S, Jamorski MT, Webb GD, Siu SC. Outcomes in adults with bicuspid aortic valves. JAMA 2008;300:1317–1325.
65. Aicher D, Langer F, Lausberg H, Bierbach B, Scha¨fers HJ. Aortic root remodeling: ten-year experience with 274 patients. J Thorac Cardiovasc Surg 2007;134: 909–915.
66. Aicher D, Fries R, Rodionycheva S, Schmidt K, Langer F, Scha¨fers HJ. Aortic valve repair leads to a low incidence of valve-related complications. Eur J Cardiothorac Surg 2010;37:127–132.
67. Boodhwani M, de Kerchove L, Glineur D, Rubay J, Vanoverschelde JL, Van Dyck M, Noirhomme P, El Khoury G. Aortic valve repair with ascending aortic aneurysms: associated lesions and adjunctive techniques. Eur J Cardiothorac Surg 2011;40:424–428.
68. Takkenberg JJ, Klieverik LM, Schoof PH, van Suylen RJ, van Herwerden LA, Zondervan PE, Roos-Hesselink JW, Eijkemans MJ, Yacoub MH, Bogers AJ. The Ross procedure: a systematic review and meta-analysis. Circulation 2009;119: 222–228.
69. Tornos MP, Sambola A, Permanyer-Miralda G, Evangelista A, Gomez Z, Soler-Soler J. Long-term outcome of surgically treated aortic regurgitation: influence of guideline adherence toward early surgery. J Am Coll Cardiol 2006;47: 1012–1017.
70. Klodas E, Enriquez-Sarano M, Tajik AJ, Mullany CJ, Bailey KR, Seward JB. Aortic regurgitation complicated by extreme left ventricular dilatation: long-term outcome after surgical correction. J Am Coll Cardiol 1996;27:670–677.
71. Chaliki HP, Mohty D, Avierinos J-F, Scott CG, Schaff HV, Tajik AJ, Enriquez-Sarano M. Outcomes after aortic valve replacement in patients with severe aortic regurgitation and markedly reduced left ventricular function. Circulation 2002;106:2687–2693. ESC/EACTS Guidelines 2491
72. Meijboom LJ, Vos FE, Timmermans J, Boers GH, Zwinderman AH, Mulder B. Pregnancy and aortic root growth in the Marfan syndrome: a prospective study. Eur Heart J 2005;26:914–920.
73. Davies RR, Gallo A, Coady MA, Tellides G, Botta DM, Burke B, Coe MP, Kopf GS, Elefteriades JA. Novel measurement of relative aortic size predicts rupture of thoracic aortic aneurysms. Ann Thorac Surg 2006;81:169–177.
74. Borger MA, Preston M, Ivanov J, Fedak PW, Davierwala P, Armstrong S, David TE. Should the ascending aorta be replaced more frequently in patients with bicuspid aortic valve disease? J Thorac Cardiovasc Surg 2004;128:677–683.
75. Evangelista A, Tornos P, Sambola A, Permanyer-Miralda G, Soler-Soler J. Longterm vasodilator therapy in patients with severe aortic regurgitation. N Engl J Med 2005;353:1342–1349.
76. Minners J, Allgeier M, Gohlke-Baerwolf C, Kienzle RP, Neumann FJ, Jander N. Inconsistencies of echocardiographic criteria for grading of aortic valve stenosis. Eur Heart J 2008;29:1043–1048
77. de Filippi CR, Willett DL, Brickner ME, Appleton CP, Yancy CW, Eichhorn EJ, Grayburn PA. Usefulness of dobutamine echocardiography in distinguishing severe from nonsevere valvular aortic stenosis in patients with depressed left ventricular function and low transvalvular gradients. Am J Cardiol 1995;75: 191–194.
78. Levy F, Laurent M, Monin JL, Maillet JM, Pasquet A, Le Tourneau T, Petit-Eisenmann H, Gori M, Jobic Y, Bauer F, Chauvel C, Leguerrier A, Tribouilloy C. Aortic valve replacement for low-flow/low-gradient aortic stenosis operative risk stratification and long-term outcome: a European multicenter study. J Am Coll Cardiol 2008;51:1466–1472.
79. Jander N, Minners J, Holme I, Gerdts E, Boman K, Brudi P, Chambers JB, Egstrup K, Kesa¨niemi YA, Malbecq W, Nienaber CA, Ray S, Rossebø A, Pedersen TR, Skjærpe T, Willenheimer R, Wachtell K, Neumann F-J, Gohlke-Ba¨rwolf C. Outcome of patients with low-gradient 'severe' aortic stenosis and preserved ejection fraction. Circulation 2011;123:887–895.
80. Lancellotti P, Lebois F, Simon M, Tombeux C, Chauvel C, Pierard LA. Prognostic importance of quantitative exercise: Doppler echocardiography in asymptomatic valvular aortic stenosis. Circulation 2005; 112(9 Suppl):pI-377–382.
81. Maréchaux S, Hachicha Z, Bellouin A, Dumesnil JG, Meimoun P, Pasquet A, Bergeron S, Arsenault M, Le Tourneau T, Ennezat PV, Pibarot P. Usefulness of exercise-stress echocardiography for risk stratification of true asymptomatic patients with aortic valve stenosis. Eur Heart J 2010;31:1390–1397.
82. Zamorano JL, Badano LP, Bruce C, Chan KL, Gonc¸alves A, Hahn RT, Keane MG, La Canna G, Monaghan MJ, Nihoyannopoulos P, Silvestry FE, Vanoverschelde J-L, Gillam LD. EAE/ASE recommendations for the use of echocardiography in new transcatheter interventions for valvular heart disease Eur Heart J 2011;32: 2189–2214.
83. Rafique AM, Biner S, Ray I, Forrester JS, Tolstrup K, Siegel RJ. Meta-analysis of prognostic value of stress testing in patients with asymptomatic severe aortic stenosis. Am J Cardiol 2009;104:972–977.
84. Azevedo CF, Nigri M, Higuchi ML, Pomerantzeff PM, Spina GS, Sampaio RO, Tarasoutchi F, Grinberg M, Rochitte CE. Prognostic significance of myocardial fibrosis quantification by histopathology and magnetic resonance imaging in patients with severe aortic valve disease. J Am Coll Cardiol 2010;56:278–287.
85. Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, Binder T, Pacher R, Maurer G, Baumgartner H. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. Circulation 2004; 109:2302–2308.
86. Monin JL, Lancellotti P, Monchi M, Lim P, Weiss E, Pie´rard L, Gue´ret P, Risk score for predicting outcome in patients with asymptomatic aortic stenosis. Circulation 2009;120:69–75.
87. Lancellotti P, Moonen M, Magne J, O'Connor K, Cosyns B, Attena E, Donal E, Pierard L. Prognostic effect of long-axis left ventricular dysfunction and B-type natriuretic peptide levels in asymptomatic aortic stenosis. Am J Cardiol 2010; 105:383–388.
88. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, Kraft CD, Miyake-Hull CY, Schwaegler RG. Prospective study of asymptomatic valvular aortic stenosis clinical, echocardiographic and exercise predictors of outcome. Circulation 1997;95:2262–2270.
89. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe, asymptomatic aortic stenosis. N Engl J Med 2000;343:611–617.
90. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. Circulation 2005;111: 3290–3295.
91. Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, Bergler-Klein J, Grimm M, Gabriel H, Maurer G. Natural history of very severe aortic stenosis. Circulation 2010;121:151–156.
92. Cioffi G, Faggiano P, Vizzardi E, Tarantini L, Cramariuc D, Gerdts E, de Simone G. Prognostic value of inappropriately high left ventricular mass in asymptomatic severe aortic stenosis. Heart 2011;97:301–307.
93. Das P, Rimington H, Chambers J. Exercise testing to stratify risk in aortic stenosis. Eur Heart J 2005;26:1309–1313.
94. Brown JM, O'Brien SM, Wu C, Sikora JAH, Griffith BP, Gammie JS. Isolated aortic valve replacement in North America comprising 108,687 patients in 10 years: changes in risks, valve types, and outcomes in the Society of Thoracic Surgeons National Database. J Thorac Cardiovasc Surg 2009;137:82–90.
95. El Bardissi AW, Shekar P, Couper GS, Cohn LH. Minimally invasive aortic valve replacement in octogenarian, high-risk, transcatheter aortic valve implantation candidates. J Thorac Cardiovasc Surg 2011;141:328–335.
96. Chukwuemeka A, Borger MA, Ivanov J, Armstrong S, Feindel C, David T. Valve surgery in octogenarians: a safe option with good medium-term results. J Heart Valve Dis 2006;15:191–196.
97. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Williams M, Dewey T,

Kapadia S, Babaliaros V, Thourani VH, Corso P, Pichard AD, Bavaria JE, Herrmann HC, Akin JJ, Anderson WN,Wang D, Pocock SJ; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187–2198.

98. Tissot CM, Attias D, Himbert D, Ducrocq G, Iung B, Dilly MP, Juliard JM, Lepage L, Détaint D, Messika-Zeitoun D, Nataf P, Vahanian A. Reappraisal of percutaneous aortic balloon valvuloplasty as a preliminary treatment strategy in the transcatheter aortic valve implantation era. EuroIntervention 2011;7:49–56.
99. Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, Tuzcu EM, Webb JG, Fontana GP, Makkar RR, Brown DL, Block PC, Guyton RA, Pichard AD, Bavaria JE, Herrmann HC, Douglas PS, Petersen JL, Akin JJ, Anderson WN,Wang D, Pocock S; PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597–1607.
100. Thomas M, Schymik G, Walther Th, Himbert D, Lefe`vre Th, Treede H, Eggebrecht H, Rubino P, Michev I, Lange R, Anderson WN, Wendler O, on behalf of the SOURCE Investigators. Thirty-day results of the SAPIEN aortic bioprosthesis European outcome (SOURCE) registry: a European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2010;122:62–69.
101. Piazza N, Grube E, Gerckens U, den Heijer P, Linke A, Luha O, Ramondo A, Ussia G, Wenaweser P, Windecker S, Laborde JC, de Jaegere P, Serruys PW. Procedural and 30-day outcomes following transcatheter aortic valve implantation using the third generation (18 Fr) corevalve revalving system: results from the multicentre, expanded evaluation registry 1-year following CE mark approval. EuroIntervention 2008;4:242–249.
102. Thomas M, Schymik G, Walther T, Himbert D, Lefe`vre T, Treede H, Eggebrecht H, Rubino P, Colombo A, Lange R, Schwarz RR, Wendler O. One-year outcomes of cohort 1 in the Edwards SAPIEN Aortic Bioprosthesis European Outcome (SOURCE) registry: the European registry of transcatheter aortic valve implantation using the Edwards SAPIEN valve. Circulation 2011;124: 425–433.
103. Zahn R, Gerckens U, Grube E, Linke A, Sievert H, Eggebrecht H, Hambrecht R, Sack S, Hauptmann KE, Richardt G, Figulla HR, Senges J; The German transcatheter aortic valve interventions: registry investigators. Transcatheter aortic valve implantation: first results from a multi-centre real-world registry. Eur Heart J 2011;32:198–204.
104. Eltchaninoff H, Prat A, Gilard M, Leguerrier A, Blanchard D, Fournial G, Iung B, Donzeau-Gouge P, Tribouilloy C, Debrux JL, Pavie A, Gueret P; FRANCE Registry Investigators. Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry. Eur Heart J 2011;32:191–197.
105. Tamburino C, Capodanno D, Ramondo A, Petronio AS, Ettori F, Santoro G, Klugmann S, Bedogni F, Maisano F, Marzocchi A, Poli A, Antoniucci D, Napodano M, De Carlo M, Fiorina C, Ussia GP. Incidence and predictors of early and late mortality after transcatheter aortic valve implantation in 663 patients with severe aortic stenosis. Circulation 2011;123:299–308.
106. Rode´s-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Feindel CM, Osten M, Natarajan MK, Velianou JL, Martucci G, DeVarennes B, Chisholm R, Peterson MD, Lichtenstein SV, Nietlispach F, Doyle D, DeLarochellie`re R, Teoh K, Chu V, Dancea A, Lachapelle K, Cheema A, Latter D, Horlick E. Transcatheter aortic valve implantation for the treatment of severe symptomatic aortic stenosis in patients at very high or prohibitive surgical risk: acute and late outcomes of the multicenter Canadian experience. J Am Coll Cardiol 2010; 55:1080–1090.
107. Buellesfeld L, Gerckens U, Schuler G, Bonan R, Kovac J, Serruys PW, Labinaz M, den Heijer P, Mullen M, Tymchak W, Windecker S, Mueller R, Grube E. Two-year follow-up of patients undergoing transcatheter aortic valve 2492 ESC/EACTS Guidelines implantation using a self-expanding valve prosthesis. J Am Coll Cardiol 2011;57: 1650–1657.
108. Gurvitch R, Wood DA, Tay EL, Leipsic J, Ye J, Lichtenstein SV, Thompson CR, Carere RG, Wijesinghe N, Nietlispach F, Boone RH, Lauck S, Cheung A, Webb JG. Transcatheter aortic valve implantation: durability of clinical and hemodynamic outcomes beyond 3 years in a large patient cohort. Circulation 2010;122:1319–1327.
109. Leon MB, Piazza N, Nikolsky E, Blackstone EH, Cutlip DE, Kappetein AP, Krucoff MW, Mack M, Mehran R, Miller C, Morel MA, Petersen J, Popma JJ, Takkenberg JJM, Vahanian A, van Es GA, Vranckx P, Webb JG, Windecker S, Serruys PW. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. Eur Heart J 2011;32:205–217.
110. Tribouilloy C, Le´vy F, Rusinaru D, Gue´ret P, Petit-Eisenmann H, Baleynaud S, Jobic Y, Adams C, Lelong B, Pasquet A, Chauvel C, Metz D, Que´re´ JP, Monin JL. Outcome after aortic valve replacement for low-flow/low-gradient aortic stenosis without contractile reserve on dobutamine stress echocardiography. J Am Coll Cardiol 2009;53:1865–1873.
111. Brown ML, Pellikka PA, Schaff HV, Scott CG, Mullany CJ, Sundt TM, Dearani JA, Daly RC, Orszulak TA. The benefits of early valve replacement in asymptomatic patients with severe aortic stenosis. J Thorac Cardiovasc Surg 2008;135:308–315.
112. Kang DH, Park SJ, Rim JH, Yun SC, Kim DH, Song JM, Choo SJ, Park SW, Song JK, Lee JW, Park PW. Early surgery versus conventional treatment in asymptomatic very severe aortic stenosis. Circulation 2010;121:1502–1509.
113. Vahanian A, Alfieri O, Al-Attar N, Antunes M, Bax J, Cormier B, Cribier A, De Jaegere P, Fournial G, Kappetein AP, Kovac J, Ludgate S, Maisano F, Moat N, Mohr F, Nataf P, Pie´rard L, Pomar JL, Schofer J, Tornos P, Tuzcu M, van Hout B, Von Segesser LK, Walther T. Transcatheter valve implantation for patients with aortic stenosis: a position statement from the European Association of Cardio-Thoracic Surgery (EACTS) and the European Society of Cardiology (ESC), in collaboration with the European Association of Percutaneous Cardiovascular Interventions (EAPCI) Eur Heart J 2008;29:1463–1470.
114. Rossebø AB, Pedersen TR, Boman K, Brudi Ph, Chambers JB, Egstrup K, Gerdts E, Gohlke-Bärwolf Ch, Holme I, Kesäniemi YA, Malbecq W, Nienaber CA, Ray S, Skjærpe T, Wachtell K, Willenheimer R; the SEAS Investigators. Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 2008;359:1343–1356.
115. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J; ASTRONOMER Investigators. Effect of lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation 2010;121:306–314.
116. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren WMM, Albus C, Benlian P, Boysen G, Cifkova R, Deaton C, Ebrahim S, Fisher M, Germano G, Hobbs R, Hoes A, Karadeniz S, Mezzani A, Prescott E, Ryden L, Scherer M, Syvänne M, Scholte Op Reimer WJ, Vrints C, Wood D, Zamorano JL, Zannad F; Other experts who contributed to parts of the guidelines:, Cooney MT; ESC Committee for Practice Guidelines (CPG): Bax J, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S; Document Reviewers: Funck-Brentano C, Sirnes PA, Aboyans V, Ezquerra EA, Baigent C, Brotons C, Burell G, Ceriello A, De Sutter J, Deckers J, Del Prato S, Diener HC, Fitzsimons D, Fras Z, Hambrecht R, Jankowski P, Keil U, Kirby M, Larsen ML, Mancia G, Manolis AJ, McMurray J, Pajak A, Parkhomenko A, Rallidis L, Rigo F, Rocha E, Ruilope LM, van der Velde E, Vanuzzo D, Viigimaa M, Volpe M, Wiklund O, Wolpert C. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2012;33:1635–1701.
117. Smith WT 4th, Ferguson TB Jr, Ryan T, Landolfo CK, Peterson ED. Should coronary artery bypass graft surgery patients with mild or moderate aortic stenosis undergo concomitant aortic valve replacement? A decision analysis approach to the surgical dilemma. J Am Coll Cardiol 2004;44:1241–1247.

118. Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. Lancet 2009; 373:1382–1394.
119. Russo A, Suri RM, Grigioni F, Roger VL, Oh JK, Mahoney DW, Schaff HV, Enriquez-Sarano M. Clinical outcome after surgical correction of mitral regurgitation due to papillary muscle rupture. Circulation 2008;118:1528–1534.
120. Monin JL, Dehant P, Roiron C, Monchi M, Tabet JY, Clerc P, Fernandez G, Houeol R, Garot J, Chauvel C, Gueret P. Functional assessment of mitral regurgitation by transthoracic echocardiography using standardized imaging planes: diagnostic accuracy and outcome implications. J Am Coll Cardiol 2005;46: 302–309.
121. Salcedo EE, Quaife RA, Seres T, Carroll JD. A framework for systematic characterization of the mitral valve by real-time three-dimensional transesophageal echocardiography. J Am Soc Echocardiogr 2009;22:1087–1099.
122. Messika-Zeitoun D, Johnson BD, Nkomo V, Avierinos JF, Allison TG, Scott C, Tajik AJ, Enriquez-Sarano M. Cardiopulmonary exercise testing determination of functional capacity in mitral regurgitation: physiologic and outcome implications. J Am Coll Cardiol 2006;47:2521–2527.
123. Magne J, Lancellotti P, Pie´rard LA, Exercise-induced changes in degenerative mitral regurgitation. J Am Coll Cardiol 2010;56:300–309.
124. Lancellotti P, Cosyns B, Zacharakis D, Attena E, Van Camp G, Gach O, Radermecker M, Pie´rard LA. Importance of left ventricular longitudinal function and functional reserve in patients with degenerative mitral regurgitation : assessment by two-dimensional speckle tracking. J Am Soc Echocardiogr 2008;21: 1331–1336.
125. Pizarro R, Bazzino OO, Oberti PF, Falconi M, Achilli F, Arias A, Krauss JG, Cagide AM. Prospective validation of the prognostic usefulness of brain natriuretic peptide in asymptomatic patients with chronic severe mitral regurgitation. J Am Coll Cardiol 2009;54:1099–1106.
126. Klaar U, Gabriel H, Bergler-Klein J, Pernicka E, Heger M, Mascherbauer J, Rosenhek R, Binder T, Maurer G, Baumgartner. Prognostic value of serial B-type natriuretic peptide measurement in asymptomatic organic mitral regurgitation. Eur J Heart Fail 2011;13:163–169.
127. Haan CK, Cabral CI, Conetta DA, Coombs LP, Edwards FH. Selecting patients with mitral regurgitation and left ventricular dysfunction for isolated mitral valve surgery. Ann Thorac Surg 2004;78:820–825.
128. Enriquez-Sarano M, Tajik AJ, Schaff HV, Orszulak TA, McGoon MD, Bailey KR, Frye RL. Echocardiographic prediction of left ventricular function after correction of mitral regurgitation: results and clinical implications. J Am Coll Cardiol 1994;24:1536–1543.
129. Enriquez-Sarano M, Avierinos JF, Messika-Zeitoun D, Detaint D, Capps M, Nkomo V, Scott C, Schaff HV, Tajik AJ. Quantitative determinants of the outcome of asymptomatic mitral regurgitation. N Engl J Med 2005;352:875–883.
130. Barbieri A, Bursi F, Grigioni F, Tribouilloy C, Avierinos JF, Michelina HI, Rusinaru D, Szymansky C, Russo A, Suri R, Bacchi-Regiani ML, Branzi A, Modena MG, Enriquez-Sarano M; Mitral Regurgitation International DAtabase (MIDA) Investigators. Prognostic and therapeutic implications of pulmonary hypertension complicating degenerative mitral regurgitation due to flail leaflet: a multicenter long-term international study. Eur Heart J 2011;32:751–759.
131. Tribouilloy C, Grigioni F, Avierinos JF, Barbieri A, Rusinaru D, Szymanski C, Ferlito M, Tafanelli L, Bursi F, Trojette F, Branzi A, Habib G, Modena MG, Enriquez-Sarano M; MIDA Investigators. Survival implication of left ventricular end-systolic diameter in mitral regurgitation due to flail leaflets: a long-term follow-up multicenter study. J Am Coll Cardiol 2009;54:1961–1968.
132. Le Tourneau T, Messika-Zeitoun D, Russo A, Detaint D, Topilsky Y, Mahoney DW, Suri R, Enriquez-Sarano M. Impact of left atrial volume on clinical outcome in organic mitral regurgitation. J Am Coll Cardiol 2010;56:570–578.
133. Grigioni F, Tribouilloy C, Avierinos JF, Barbieri A, Ferlito M, Trojette F, Tafanelli L, Branzi A, Szymanski C, Habib G, Modena MG, Enriquez-Sarano M. Outcomes in mitral regurgitation to flail leaflets: a multicenter European study. JACC: Cardiovascular Imaging 2008;1:133–141.
134. David TE, Ivanov J, Armstrong S, Christie D, Rakowski H. A comparison of outcomes of mitral valve repair for degenerative disease with posterior, anterior, and bileaflet prolapse. J Thorac Cardiovasc Surg 2005;130:1242–1249.
135. Gammie JS, Sheng S, Griffith BP, Peterson ED, Rankin JS, O'Brien S, Brown JM. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Ann Thorac Surg 2009;87: 1431–1439.
136. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364:1395–1406.
137. Franzen O, Baldus S, Rudolph V, Meyer S, Knap M, Koschyk D, Treede H, Barmeyer A, Schofer J, Costard-Ja¨ckle A, Schlu´´ter M, Reichenspurner H, Meinertz T. Acute outcomes of MitraClip therapy for mitral regurgitation in high-surgical-risk patients: emphasis on adverse valve morphology and severe left ventricular dysfunction. Eur Heart J 2010;31:1373–1381.
138. Rosenhek R, Rader F, Klaar U, Gabriel H, Krej M, Kalbeck D, Schemper M, Maurer G, Baumgartner H. Outcome of watchful waiting in asymptomatic severe mitral regurgitation. Circulation 2006;113:2238–2244.
139. Kang DH, Kim JH, Rim JH, Kim MJ, Yun SC, Song JM, Song H, Choi KJ, Song JK, Lee JW. Comparison of early surgery versus conventional treatment in asymptomatic severe mitral regurgitation. Circulation 2009;119:797–804. ESC/EACTS Guidelines 2493
140. Samad Z, Kaul P, Shaw LK, Glower DD, Velazquez EJ, Douglas PS, Jollis JG. Impact of early surgery on survival of patients with severe mitral regurgitation. Heart 2011;97:221–224.
141. Piérard LA, Lancellotti P. The role of ischemic mitral regurgitation in the pathogenesis of acute pulmonary edema. N Engl J Med 2004;351:1627–1634.
142. Grigioni F, Enriquez-Sarano, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103:1759–1764.
143. Lancellotti P, Ge´rard P, Pie´rard L. Long term outcome of patients with heart failure and dynamic functional mitral regurgitation. Eur Heart J 2005;26: 1528–1532.
144. Gisbert A, Soulière V, Denault AY, Bouchard D, Couture P, Pellerin M, Carrier M, Levesque S, Ducharme A, Basmadjian AJ. Dynamic quantitative echocardiographic evaluation of mitral regurgitation in the operating department. J Am Soc Echocardiogr 2006;19:140–146.
145. Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003;91;538–543.
146. McGee EC Jr, Gillinov AM, Blackstone EH, Rajeswaran J, Cohen G, Najam F, Shiota T, Sabik JF, Lytle BW, McCarthy PM, Cosgrove DM. Recurrent mitral regurgitation after annuloplasty for functional ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2004;128:916–924.
147. Fattouch K, Sampognaro R, Speziale G, Salardino M, Novo G, Caruso M, Novo S, Ruvolo G. Impact of moderate ischemic mitral regurgitation after isolated coronary artery bypass grafting. Ann Thorac Surg 2010;90:1187–1194.
148. Mihaljevic T, Lam BK, Rajeswaran J, Takagaki M, Lauer MS, Gillinov AM, Blackstone EH, Lytle BW. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. J Am Coll Cardiol 2007;49:2191–2201.
149. Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol 2005;45:381–387.
150. Fattouch K, Guccione F, Sampognaro S, Panzarella G, Corrado E, Navarra E, Calvaruso D, Ruvolo G. Efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: a randomized trial. J Thorac Cardiovasc Surg 2009;138: 278–285.
151. Braun J, Bax JJ, Versteegh MI, Voigt PG, Holman ER, Klautz RJ, Boersma E, Dion RA. Preoperative left ventricular dimensions

predict reverse remodelling following restrictive mitral annuloplasty in ischaemic mitral regurgitation. Eur J Cardiothorac Surg 2005;27:847–853.
152. Ciarka A, Braun J, Delgado V, Versteegh M, Boersma E, Klautz R, Dion R, Bax JJ, Van de Veire N. Predictors of mitral regurgitation recurrence in patients with heart failure undergoing mitral valve annuloplasty. Am J Cardiol 2010;106: 395–401.
153. Acker MA, Jessup M, Bolling SF, Oh J, Starling RC, Mann DL, Sabbah HN, Shemin R, Kirklin J, Kubo SH. Mitral valve repair in heart failure: five-year followup from the mitral valve replacement stratum of the Acorn randomized trial. J Thorac Cardiovasc Surg 2011;142:569–574.
154. Pu M, Thomas JD, Gillinov MA, Griffin BP, Brunken RC. Importance of ischemic and viable myocardium for patients with chronic ischemic mitral regurgitation and left ventricular dysfunction. Am J Cardiol 2003;92:862–864.
155. Vassileva CM, Boley T, Markwell S, Hazelrigg S. Meta-analysis of short-term and long-term survival following repair versus replacement for ischemic mitral regurgitation. Eur J Cardiothorac Surg 2011;39:295–303.
156. Langer F, Kunihara T, Hell K, Schramm R, Schmidt KI, Aicher D, Kindermann M, Schäfers H-J. Ring+string: successful repair technique for ischemic mitral regurgitation with severe leaflet tethering. Circulation 2009;120(11 Suppl):S85–S91.
157. Grossi EA, Patel N, Woo YJ, Goldberg JD, Schwartz CF, Subramanian V, Feldman T, Bourge R, Baumgartner N, Genco C, Goldman S, Zenati M, Wolfe JA, Mishra YK, Trehan N, Mittal S, Shang S, Mortier TJ, Schweich CJ Jr; RESTOR-MV Study Group. Outcomes of the RESTOR-MV trial (Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve). J Am Coll Cardiol 2010;56:1984–1993.
158. Schofer J, Siminiak T, Haude M, Herrman JP, Vainer J, Wu JC, Levy WC, Mauri L, Feldman T, Kwong RY, Kaye DM, Duffy SJ, Tübler T, Degen H, Brandt MC, Van Bibber R, Goldberg S, Reuter DG, Hoppe UC. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. Circulation 2009;120:326–333.
159. van Bommel RJ, Marsan NA, Delgado V, Borleffs CJW, van Rijnsoever EPM, Schalij MJ, Bax JJ. Cardiac resynchronization therapy as a therapeutic option in patients with moderate-severe functional mitral regurgitation and high operative risk. Circulation 2011;124:912–919.
160. Bouleti C, Iung B, Laoue´nan C, Himbert D, Brochet E, Messika-Zeitoun D, Détaint D, Garbarz E, Cormier B, Michel PL, Mentré F, Vahanian A. Late results of percutaneous mitral commissurotomy up to 20 years. Development and validation of a risk score predicting late functional results from a series of 912 patients. Circulation 2012;125:2119–2127.
161. Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. Br Heart J 1988;60: 299–308.
162. Messika-Zeitoun D, Brochet E, Holmin C, Rosenbaum D, Cormier B, Serfaty JM, Iung B, Vahanian A. Three-dimensional evaluation of the mitral valve area and commissural opening before and after percutaneous mitral commissurotomy in patients with mitral stenosis. Eur Heart J 2007;28:72–79.
163. Chiang CW, Lo SK, Ko YS, Cheng NJ, Lin PJ, Chang CH, Predictors of systemic embolism in patients with mitral stenosis. A prospective study. Ann Intern Med 1998;128:885–889.
164. Iung B, Nicoud-Houel A, Fondard O, Hafid Akoudad, Haghighat T, Brochet E, Garbarz E, Cormier B, Baron G, Luxereau P, Vahanian A. Temporal trends in percutaneous mitral commissurotomy over a 15-year period. Eur Heart J 2004;25:701–707.
165. Varma PK, Theodore S, Neema PK, Ramachandran P, Sivadasanpillai H, Nair KK, Neelakandhan KS. Emergency surgery after percutaneous transmitral commissurotomy: operative versus echocardiographic findings, mechanisms of complications, and outcomes. J Thorac Cardiovasc Surg 2005;130:772–776.
166. Ben Farhat M, Ayari M, Maatouk F, Betbout F, Gamra H, Jarra M, Tiss M, Hammami S, Thaalbi R, Addad F. Percutaneous balloon versus surgical closed and open mitral commissurotomy: seven-year follow-up results of a randomized trial. Circulation 1998;97:245–250.
167. Fawzy ME, Shoukri M, Al Buraiki J, Hassan W, El Widaa H, Kharabsheh S, Al Sanei A, Canver C. Seventeen years' clinical and echocardiographic follow up of mitral balloon valvuloplasty in 520 patients, and predictors of long-term outcome. J Heart Valve Dis 2007;16:454–460.
168. Kim MJ, Song JK, Song JM, Kang DH, Kim YH, Lee CW, Hong MK, Kim JJ, Park SW, Park SJ. Long-term outcomes of significant mitral regurgitation after percutaneous mitral valvuloplasty. Circulation 2006;114:2815–2822.
169. Song J-K, Song J-M, Kang D-H, Yun S-C, Park DW, Lee SW, Kim Y-H, Lee CW, Hong M-K, Kim J-J, Park S-W, Park S-J. Restenosis and adverse clinical events after successful percutaneous mitral valvuloplasty: immediate post-procedural mitral valve area as an important prognosticator Eur Heart J 2009;30:1254–1262.
170. Cruz-Gonzalez I, Sanchez-Ledesma M, Sanchez PL, Martin-Moreiras J, Jneid H, Rengifo-Moreno P, Inglessis-Azuaje I, Maree AO, Palacios IF. Predicting success and long-term outcomes of percutaneous mitral valvuloplasty: a multifactorial score. Am J Med 2009;122:581.e11–e19.
171. Antunes MJ, Vieira H, Ferra˜o de Oliveira J. Open mitral commissurotomy: the 'golden standard'. J Heart Valve Dis 2000;9:472–477.
172. Song JK, Kim MJ, Yun SC, Choo SJ, Song JM, Song H, Kang DH, Chung CH, Park DW, Lee SW, Kim YH, Lee CW, Hong MK, Kim JJ, Lee JW, Park SW, Park SJ. Long-term outcomes of percutaneous mitral balloon valvuloplasty versus open cardiac surgery. J Thorac Cardiovasc Surg 2010;139:103–110.
173. Iung B, Garbarz E, Doutrelant L, Berdah P, Michaud P, Farah B, Mokhtari M, Makita Y, Michel PL, Luxereau P, Cormier B, Vahanian A. Late results of percutaneous mitral commissurotomy for calcific mitral stenosis. Am J Cardiol 2000;85: 1308–1314.
174. Keenan NG, Cueff C, Cimidavella C, Brochet E, Lepage L, Detaint D, Himbert D, Iung B, Vahanian A, Messika-Zeitoun D. Usefulness of left atrial volume versus diameter to assess thromboembolic risk in mitral stenosis. Am J Cardiol 2010; 106:1152–1156.
175. Fawzy ME, Hassan W, Shoukri M, Al Sanei A, Hamadanchi A, El Dali A, Al Amri M. Immediate and long-term results of mitral balloon valvotomy for restenosis following previous surgical or balloon mitral commissurotomy. Am J Cardiol 2005;96:971–975.
176. Kim JB, Ha JW, Kim JS, Shim WH, Kang SM, Ko YG, Choi D, Jang Y, Chung N, Cho SY, Kim SS. Comparison of long term outcome after mitral valve replacement or repeated balloon valvotomy in patients with restenosis after previous balloon valvotomy. Am J Cardiol 2007;99:1571–1574.
177. Song H, Kang DH, Kim JH, Park K-M, Song J-M, Choi K-J, Hong M-K, Chung CH, Song J-K, Lee J-W, Park S-W, Park S-J. Percutaneous mitral valvuloplasty versus surgical treatment in mitral stenosis with severe tricuspid regurgitation. Circulation 2007;116(11 Suppl):I246–250.
178. Colombo T, Russo C, Ciliberto GR, Lanfranconi M, Bruschi G, Agati S, Vitali E. Tricuspid regurgitation secondary to mitral valve disease: tricuspid annulus function as guide to tricuspid valve repair. Cardiovas Surg 2001;9:369–377.
179. Dreyfus GD, Corbi PJ, Chan KM, Bahrami T. Secondary tricuspid regurgitation or dilatation: which should be the criteria for surgical repair? Ann Thorac Surg 2005;79:127–132.
180. Van de Veire NR, Braun J, Delgado V, Versteegh MI, Dion RA, Klautz RJ, Bax JJ. Tricuspid annuloplasty prevents right ventricular dilatation and progression of 2494 ESC/EACTS Guidelines tricuspid regurgitation in patients with tricuspid annular dilatation undergoing mitral valve repair. J Thorac Cardiovasc Surg 2011;141:1431–1439.
181. Fukuda S, Gillinov AM, McCarthy PM, Stewart WJ, Song JM, Kihara T, Daimon M, Shin MS, Thomas JD, Shiota T. Determinants of recurrent or residual functional tricuspid regurgitation after tricuspid annuloplasty. Circulation 2006;114(1 Suppl): I582–587.
182. Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. Circulation 2008;117:1717–1731.
183. Nath J, Foster E, Heidenreich PA. Impact of tricuspid regurgitation on long-term survival. J Am Coll Cardiol 2004;43:405–409.
184. Messika-Zeitoun D, Thomson H, Bellamy M, Scott C, Tribouilloy C, Dearani J, Tajik AJ, Schaff H, Enriquez-Sarano M. Medical and

surgical outcome of tricuspid regurgitation caused by flail leaflets. J Thorac Cardiovasc Surg 2004;128:296–302.
185. McCarthy PM, Bhudia SK, Rajeswaran J, Hoercher KJ, Lytle BW, Cosgrove DM, Blackstone EH. Tricuspid valve repair: durability and risk factors for failure. J Thorac Cardiovasc Surg 2004;127:674–685.
186. Navia JL, Nowicki ER, Blackstone EH, Brozzi NA, Nento DE, Atik FA, Rajeswaran J, Gillinov AM, Svensson LG, Lytle BW. Surgical management of secondary tricuspid valve regurgitation: annulus, commissure, or leaflet procedure? J Thorac Cardiovasc Surg 2010;139:1473–1482.
187. Tang GH, David TE, Singh SK, Maganti MD, Armstrong S, Borger MA. Tricuspid valve repair with an annuloplasty ring results in improved long-term outcomes. Circulation 2006;114(1 Suppl):I577–581.
188. Dreyfus GD, Raja SG, John Chan KM. Tricuspid leaflet augmentation to address severe tethering in functional tricuspid regurgitation. Eur J Cardiothorac Surg 2008; 34:908–910.
189. Chang BC, Lim SH, Yi G, Hong YS, Lee S, Yoo KJ, Kang M S, Cho BK. Long-term clinical results of tricuspid valve replacement. Ann Thorac Surg 2006;81: 1317–1323.
190. Unger P, Rosenhek R, Dedobbeleer C, Berrebi A, Lancellotti P. Management of multiple valve disease. Heart 2011;97:272–277.
191. Filsoufi F, Anyanwu AC, Salzberg SP, Frankel T, Cohn LH, Adams DH. Long-term outcomes of tricuspid valve replacement in the current era. Ann Thorac Surg 2005;80:845–850.
192. Yeter E, Ozlem K, Kiliç H, Ramazan A, Acikel S. Tricuspid balloon valvuloplasty to treat tricuspid stenosis. J Heart Valve Dis 2010;19:159–160.
193. De Kerchove L, Glineur D, El Khoury G, Noirhomme P. Stentless valves for aortic valve replacement: where do we stand? Curr Opin Cardiol 2007;22:96–130.
194. Smedira NG, Blackstone EH, Roselli EE, Laffey CC, Cosgrove DM. Are allografts the biologic valve of choice for aortic valve replacement in nonelderly patients? Comparison of explantation for structural valve deterioration of allograft and pericardial prostheses. J Thorac Cardiovasc Surg 2006;131:558–564.
195. El-Hamamsy I, Clark L, Stevens LM, Sarang Z, Melina G, Takkenberg JJ, Yacoub MH. Late outcomes following freestyle versus homograft aortic root replacement: results from a prospective randomized trial. J Am Coll Cardiol 2010; 55:368–376.
196. Nowicki ER, Pettersson GB, Smedira NG, Roselli EE, Blackstone EH, Lytle BW. Aortic allograft valve reoperation: surgical challenges and patient risks. Ann Thorac Surg 2008;86:761–768.
197. Byrne JG, Rezai K, Sanchez JA, Bernstein RA, Okum E, Leacche M, Balaguer JM, Prabhakaran S, Bridges CR, Higgins RSD . Surgical Management of Endocarditis: The Society of Thoracic Surgeons Clinical Practice Guideline. Ann Thorac Surg 2011;91:2012–2019.
198. El-Hamamsy I, Eryigit Z, Stevens LM, Sarang Z, George R, Clark L, Melina G, Takkenberg JJ, Yacoub MH. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet 2010;376:524–531.
199. Hammermeister K, Sethi GK, Henderson WG, Grover FL, Oprian C, Rahimtoola SH. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol 2000;36:1152–1158.
200. Oxenham H, Bloomfield P, Wheatley DJ, Lee RJ, Cunningham J, Prescott RJ, Miller HC. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. Heart 2003;89:715–721.
201. Stassano P, Di Tommaso L, Monaco M, Iorio F, Pepino P, Spampinato N, Vosa C. Aortic valve replacement: a prospective randomized evaluation of mechanical versus biological valves in patients ages 55 to 70 years. J Am Coll Cardiol 2009; 54:1862–1868.
202. Stoica S, Goldsmith K, Demiris N, Punjabi P, Berg G, Sharples L, Large S. Microsimulation and clinical outcomes analysis support a lower age threshold for use of biological valves. Heart 2010;96:1730–1736.
203. Butchart EG, Gohlke-Ba¨rwolf C, Antunes MJ, Tornos P, De Caterina R, Cormier B, Prendergast B, Iung B, Bjornstad H, Leport C, Hall RJC, Vahanian A. Recommendations for the management of patients after heart valve surgery Eur Heart J 2005;26:2463–2471.
204. van Geldorp MW, Eric Jamieson WR, Kappetein AP, Ye J, Fradet GJ, Eijkemans MJ, Grunkemeier GL, Bogers AJ, Takkenberg JJ. Patient outcome after aortic valve replacement with a mechanical or biological prosthesis: weighing lifetime anticoagulant-related event risk against reoperation risk. J Thorac Cardiovasc Surg 2009;137:881–886.
205. Sun JC, Davidson MJ, Lamy A, Eikelboom JW. Antithrombotic management of patients with prosthetic heart valves: current evidence and future trends. Lancet 2009;374:565–576.
206. Herzog CA, Ma JZ, Collins AJ. Long-term survival of dialysis patients in the United States with prosthetic heart valves: should ACC/AHA practice guidelines on valve selection be modified? Circulation 2002;105:1336–1341.
207. Regitz-Zagrosek V, Lundqvist CB, Borghi C, Cifkova R, Ferreira R, Foidart JM, Gibbs JS, Gohlke-Baerwolf C, Gorenek B, Iung B, Kirby M, Maas AH, Morais J, Nihoyannopoulos P, Pieper PG, Presbitero P, Roos-Hesselink JW, Schaufelberger M, Seeland U, Torracca L; ESC Committee for Practice Guidelines (CPG), Bax J, Auricchio A, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Knuuti J, Kolh P, McDonagh T, Moulin C, Poldermans D, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Torbicki A, Vahanian A, Windecker S; Document Reviewers, Baumgartner H, Deaton C, Aguiar C, Al-Attar N, Garcia AA, Antoniou A, Coman I, Elkayam U, Gomez-Sanchez MA, Gotcheva N, Hilfiker-Kleiner D, Kiss RG, Kitsiou A, Konings KT, Lip GY, Manolis A, Mebaaza A, Mintale I, Morice MC, Mulder BJ, Pasquet A, Price S, Priori SG, Salvador MJ, Shotan A, Silversides CK, Skouby SO, Stein JI, Tornos P, Vejlstrup N, Walker F, Warnes C. ESC Guidelines on the management of cardiovascular diseases during pregnancy: The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J 2011;32:3147–3197.
208. Bleiziffer S, Eichinger WB, Hettich I, Guenzinger R, Ruzicka D, Bauernschmitt R, Lange R. Prediction of valve prosthesis-patient mismatch prior to aortic valve replacement: which is the best method? Heart 2007;93:615–620.
209. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. Circulation 2009;119:1034–1048.
210. Zoghbi WA, Chambers JB, Dumesnil JG, Foster E, Gottdiener JS, Grayburn PA, Khandheria BK, Levine RA, Marx GR, Miller FA Jr., Nakatani S, Quiñones MA, Rakowski H, Rodriguez LL, Swaminathan M, Waggoner AD, Weissman NJ, Zabalgoitia M. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. J Am Soc Echocardiogr 2009;22:975–1014.
211. Symersky P, Budde RP, de Mol BA, Prokop M. Comparison of multidetector-row computed tomography to echocardiography and fluoroscopy for evaluation of patients with mechanical prosthetic valve obstruction. Am J Cardiol 2009;104: 1128–1134.
212. Salem DN, O'Gara PT, Madias C, Pauker SG. Valvular and structural heart disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133(6 Suppl):p593S–629S.
213. Cannegieter SC, Rosendaal FR, Briët E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. Circulation 1994;89: 635–641.
214. Nowell J, Wilton E, Markus H, Jahangiri M. Antithrombotic therapy following bioprosthetic aortic valve replacement. Eur J Cardiothorac Surg 2007;31:578–585.

215. Dunning J, Versteegh M, Fabbri A, Pavie A, Kolh P, Lockowandt U, Nashef SA; EACTS Audit and Guidelines Committee. Guideline on antiplatelet and anticoagulation management in cardiac surgery. Eur J Cardiothorac Surg 2008;34:73–92.
216. Rivas-Gándara N, Ferreira-González I, Tornos P, Torrents A, Permanyer- Miralda G, Nicolau I, Arellano-Rodrigo E, Vallejo N, Igual A, Soler-Soler J. Enoxaparin as bridging anticoagulant treatment in cardiac surgery. Heart 2008;94: 205–210.
217. Laplace G, Lafitte S, Labèque JN, Perron JM, Baudet E, Deville C, Roques X, Roudaut R. Clinical significance of early thrombosis after prosthetic mitral valve replacement: a postoperative monocentric study of 680 patients. J Am Coll Cardiol 2004;43:1283–1290. ESC/EACTS Guidelines 2495
218. Russo A, Grigioni F, Avierinos JF, Freeman WK, Suri R, Michelena H, Brown R, Sundt TM, Enriquez-Sarano M. Thromboembolic complications after surgical correction of mitral regurgitation incidence, predictors, and clinical implications. J Am Coll Cardiol 2008;51:1203–1211.
219. Butchart EG, Ionescu A, Payne N, Giddings J, Grunkemeier GL, Fraser AG. A new scoring system to determine thromboembolic risk after heart valve replacement. Circulation 2003;108(Suppl 1):II68–74.
220. Acar J, Iung B, Boissel JP, Samama MM, Michel PL, Teppe JP, Pony JC, Breton HL, Thomas D, Isnard R, de Gevigney G, Viguier E, Sfihi A, Hanania G, Ghannem M, Mirode A, Nemoz C. AREVA: multicenter randomized comparison of low-dose versus standard-dose anticoagulation in patients with mechanical prosthetic heart valves. Circulation 1996;94:2107–2112.
221. Hering D, Piper C, Bergemann R, Hillenbach C, Dahm M, Huth C, Horstkotte D. Thromboembolic and bleeding complications following St. Jude Medical valve replacement: results of the German Experience With Low-Intensity Anticoagulation Study. Chest 2005;127:53–59.
222. Koertke H, Zittermann A, Tenderich G, Wagner O, El-Arousy M, Krian A, Ennker J, Taborski U, Klövekorn WP, Moosdorf R, Saggau W, Koerfer R. Low-dose oral anticoagulation in patients with mechanical heart valve prostheses: final report from the early self-management anticoagulation trial II. Eur Heart J 2007;28:2479–2484.
223. Pernod G, Godiér A, Gozalo C, Tremey B, Sié P; French National Authority for Health. French clinical practice guidelines on the management of patients on vitamin K antagonists in at-risk situations (overdose, risk of bleeding, and active bleeding). Thromb Res 2010;126:e167–e174.
224. Turpie AG, Gent M, Laupacis A, Latour Y, Gunstensen J, Basile F, Klimek M, Hirsh J. A comparison of aspirin with placebo in patients treated with warfarin after heart-valve replacement. N Engl J Med 1993;329:524–529. 225. Massel D, Little SH. Risks and benefits of adding anti-platelet therapy to warfarin among patients with prosthetic heart valves: a meta-analysis. J Am Coll Cardiol 2001;37:569–578.
226. Laffort P, Roudaut R, Roques X, Lafitte S, Deville C, Bonnet J, Baudet E. Early and long-term (one-year) effects of the association of aspirin and oral anticoagulant on thrombi and morbidity after replacement of the mitral valve with the St. Jude medical prosthesis: a clinical and transesophageal echocardiographic study. J Am Coll Cardiol 2000;35:739–746.
227. Poldermans D, Bax JJ, Boersma E, De Hert S, Eeckhout E, Fowkes G, Gorenek B, Hennerici MG, Iung B, Kelm M, Kjeldsen KP, Kristensen SD, Lopez-Sendon J, Pelosi P, Philippe F, Pierard L, Ponikowski P, Schmid JP, Sellevold OF, Sicari R, Van den Berghe G, Vermassen F, Hoeks SE, Vanhorebeek I. Guidelines for preoperative cardiac risk assessment and perioperative cardiac management in noncardiac surgery: the Task Force for Preoperative Cardiac Risk Assessment and Perioperative Cardiac Management in Non-cardiac Surgery of the European Society of Cardiology (ESC) and European Society of Anaesthesiology (ESA). Eur Heart J 2009;30:2769–2812.
228. Douketis JD, Berger PB, Dunn AS, Jaffer AK, Spyropoulos AC, Becker RC, Ansell J. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:299S–339S.
229. Francophone society of oral medicine and oral surgery wtcotFsoc. Guidelines for management of patients under antivitamin K treatment in oral surgery. http://www.societechirbuc.com/Recommandations/recommandations_ avk_gb.pdf
230. Ferreira I, Dos L, Tornos P, Nicolau I, Permanyer-Miralda G, Soler-Soler J. Experience with enoxaparin in patients with mechanical heart valves who must withhold acenocumarol. Heart 2003;89:527–530.
231. Pengo V, Cucchini U, Denas G, Erba N, Guazzaloca G, La Rosa L, De Micheli V, Testa S, Frontoni R, Prisco D, Nante G, Iliceto S; Italian Federation of Centers for the Diagnosis of Thrombosis and Management of Antithrombotic Therapies (FCSA). Standardized low-molecular-weight heparin bridging regimen in outpatients on oral anticoagulants undergoing invasive procedure or surgery: an inception cohort management study. Circulation 2009;119:2920–2927.
232. Tong AT, Roudaut R, Ozkan M, Sagie A, Shahid MS, Pontes Júnior SC, Carreras F, Girard SE, Arnaout S, Stainback RF, Thadhani R, Zoghbi WA; Prosthetic Valve Thrombolysis-Role of Transesophagesophageal Echocardiography (PRO-TEE) Registry Investigators. Transesophagesophageal echocardiography improves risk assessment of thrombolysis of prosthetic valve thrombosis: results of the international PRO-TEE registry. J Am Coll Cardiol 2004;43:77–84.
233. Roudaut R, Lafitte S, Roudaut MF, Reant P, Pillois X, Durrieu-Jaïs C, Coste P, Deville C, Roques X. Management of prosthetic heart valve obstruction: fibrinolysis versus surgery. Early results and long-term follow-up in a single-centre study of 263 cases. Early results and long-term follow-up in a single-centre study of 263 cases. Arch Cardiovasc Dis 2009;102:269–277.
234. Roudaut R, Serri K, Lafitte S. Thrombosis of prosthetic heart valves: diagnosis and therapeutic considerations. Heart 2007;93:137–142.
235. Ionescu A, Fraser AG, Butchart EG. Prevalence and clinical significance of incidental paraprosthetic valvar regurgitation: a prospective study using transoesophageal echocardiography. Heart 2003;89:1316–1321.
236. Sorajja P, Cabalka AK, Hagler DJ, Rihal CS. Percutaneous repair of paravalvular prosthetic regurgitation: acute and 30-day outcomes in 115 patients. Circ Cardiovasc Interv 2011;4:314–321.
237. Jaussaud N, Gariboldi V, Giorgi R, Grisoli D, Chalvignac V, Thuny F, Riberi A, Collart F. Risk of reoperation for aortic bioprosthesis dysfunction. J Heart Valve Dis 2009;18:256–261.
238. Webb JG, Wood DA, Ye J, Gurvitch R, Masson JB, Rode´s-Cabau J, Osten M, Horlick E, Wendler O, Dumont E, Carere RG, Wijesinghe N, Nietlispach F, Johnson M, Thompson CR, Moss R, Leipsic J, Munt B, Lichtenstein SV, Cheung A. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. Circulation 2010;121:1848–1857.
239. Piazza N, Bleiziffer S, Brockmann G, Hendrick R, Deutsch M-A, Opitz A, Mazzitelli D, Tassani-Prell P, Schreiber C, Lange R. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical application and evaluation (Part 1). JACC Cardiovasc Interv 2011;4: 721–732.
240. Calleja AM, Dommaraju S, Gaddam R, Cha S, Khandheria BK, Chaliki HP. Cardiac risk in patients aged .75 years with asymptomatic, severe aortic stenosis undergoing noncardiac surgery. Am J Cardiol 2010;105:1159–1163.
241. Bradley D, Creswell LL, Hogue CW Jr, Epstein AE, Prystowsky EN, Daoud EG. Pharmacologic prophylaxis: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. Chest 2005;128:39S–47S

CARDIOHELP SYSTEM
THE MULTI-THERAPY SOLUTION

CARDIOHELP is a multi-therapy cardiopulmonary support system which can be rapidly deployed and used for a wide range of indications in intensive care, emergency medicine, cardiology and cardiac surgery.

CARDIOHELP is a compact and light weight system making it also ideal for transporting patients whilst on respiratory and / or circulatory support.

MAQUET – The Gold Standard.

MAQUET
GETINGE GROUP

MAQUET South East Europe d.o.o.
3 Spanskih boraca Street
11070 Belgrade
SERBIA
Tel: +381 11 7856370
Fax: +381 11 7856371
office@maquet.rs
www.maquet.com

MORE INFORMATION: www.maquet-cardiohelp.com

MERITMEDICAL

ANGIOGRAFSKI SET

DA LI STE SVE PRIPREMILI?

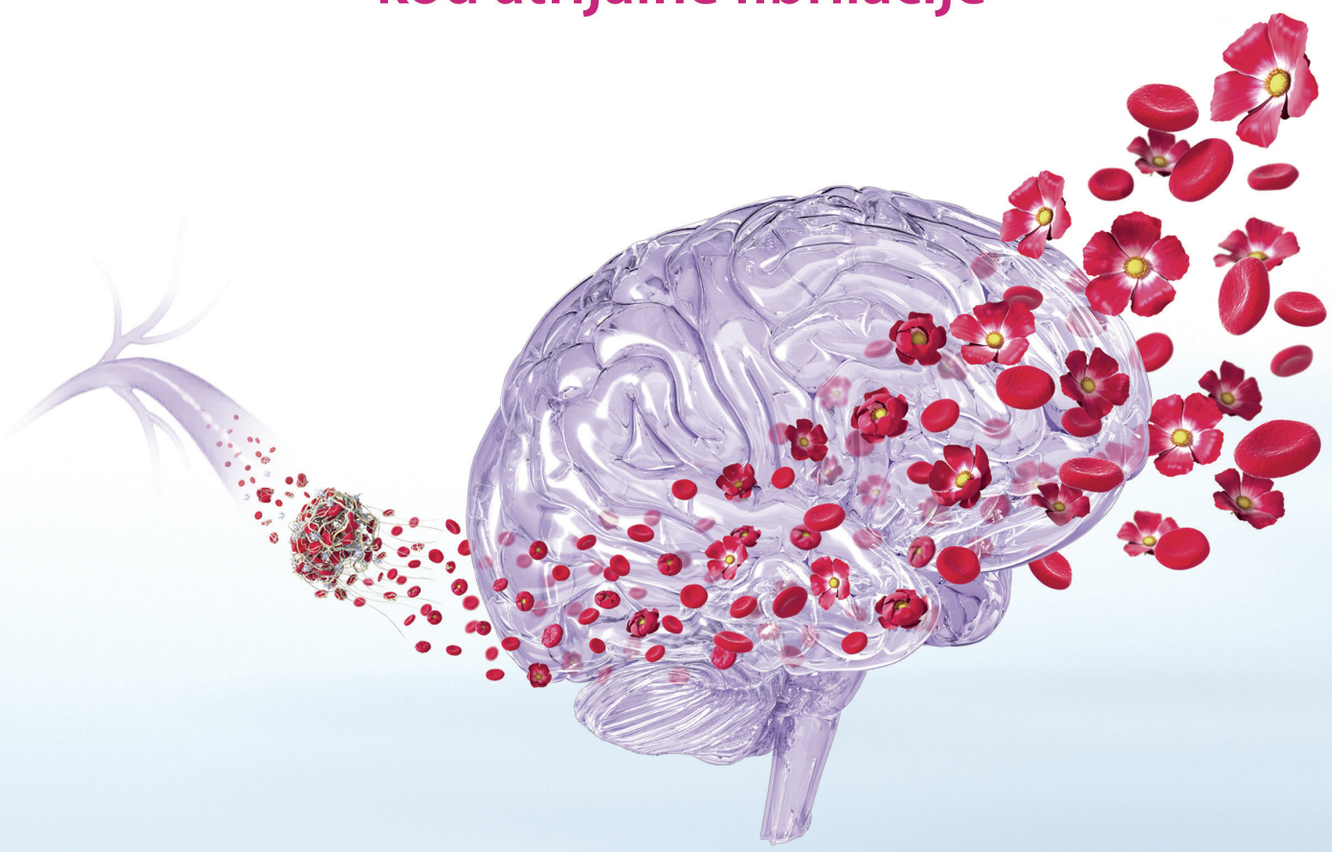
Ekskluzivni zastupnik za Srbiju:
APTUS Beograd
Tel.011/ 79 43 741, 79 43 742
aptus@vektor.net

Bayer HealthCare

Xarelto®: efikasna zaštita

1 x DNEVNO

U prevenciji moždanog udara kod atrijalne fibrilacije



Xarelto®
rivaroxaban

Samo za stručnu javnost

Način izdavanja leka: lek se može izdavati samo uz lekarski recept.
Broj i datum dozvole: Xarelto®, film tablete, 14x(15mg): 515-01-8741-11-001 od 18.04.2013.,Xarelto®, film tablete, 14x(20mg): 515-01-8742-11-001 od 18.04.2013., Xarelto®, film tablete, 28x(15mg): 515-01-3983-12-001 od 18.04.2013., Xarelto®, film tablete, 28x(20mg): 515-01-3985-12-001 od 18.04.2013. Xarelto®, film tablete, 42x(15mg): 515-01-3984-12-001 od 18.04.2013.
Nosilac dozvole: Bayer d.o.o. Omladinskih brigada 88b, 11070 Beograd

SERVIER

Life through Discovery