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Almanah 2013.: nove nekoronarne srčane intervencije

Almanac 2013: novel non-coronary cardiac interventions

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SAŽETAK: Aktualne inovacije u intervencijskoj kardiologiji dramatično su proširile terapijske mogućnosti za srčane bolesnike. Intervencijska kardiologija više nije ograničena na liječenje koronarne bolesti srca već je moguće liječiti bolesti zalistaka, raditi na prevenciji moždanog udara, liječenju arterijske hipertenzije, itd. Jedna od najvažnijih novih mogućnosti liječenja je perkutano liječenje aortne stenoze (transkateterska implantacija aortne valvule), budući da je bolest aortne valvule vrlo čest problem u bolesnika starije životne dobi, a mnogi od njih imaju visok rizik od operacije. Isto tako, mitralna regurgitacija je često povezana s pojavom komorbiditeta koji čine operaciju visokorizičnom. MitraClip je obećavajuće perkutano alternativno rješenje za kirurški popravak ili zamjenu srčanog zaliska. Ostali postupci koji se spominju u ovom preglednom članku su perkutano zatvaranje aurikule lijevog atrija kao nefarmakološka terapija za prevenciju moždanog udara, renalna denervacija za rezistentnu arterijsku hipertenziju. U ovom se članku pojašnjavaju osnovni principi ovih postupaka, najvažnije kliničke studije uz dodatne kliničke podatke o svakom od njih.

KLJUČNE RIJEČI: intervencijska kardiologija, intervencijski zahvati na zaliscima.

SUMMARY: Recent innovations in interventional cardiology have dramatically expanded the therapeutic options for patients with cardiac conditions. Interventional cardiology is no longer limited to the treatment of coronary artery disease but allows also treatment of valvular disease, stroke prevention, hypertension, etc. One of the most important new treatment options is the percutaneous treatment for aortic valve stenosis (transcatheter aortic valve implantation), since aortic valve disease is a rather common problem in elderly patients, with many of them at high risk for surgery. Similarly, mitral regurgitation is often associated with comorbidities which make surgery high risk. The MitraClip is a promising percutaneous alternative to surgical valve repair or replacement. Other procedures discussed in this review are the percutaneous left atrial appendage closure as a non-pharmacologic therapy to prevent strokes, and renal denervation for resistant hypertension. This review explains the basic principles of these procedures, the most important clinical evidence, and also provides additional recent clinical data on each of these them.

KEYWORDS: interventional cardiology, valve interventions

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Uvod

Nakon što je Andreas Gruentzig revolucionarno upotrijebio balonsku angioplastiku, perkutane koronarne intervencije su postale glavno uporište u kardiologiji u sljedećim desetljećima[1]; odnosno, sve do nedavno kada je kardiologija usvojila inovacije koje se mogu smatrati jednako revolucionarnim kao i Gruentzigova angioplastika. Ponajprije je razvoj mo-

Introduction

After Andreas Gruentzig's pioneering balloon angioplasty, percutaneous coronary interventions became the mainstay of cardiology for the ensuing decades[1]; that is until very recently when cardiology has adopted innovations which can be regarded as revolutionary as Gruentzig's angioplasty. Foremost in the development of percutaneous treatment

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gućnosti perkutanog liječenja aortne stenoze, odnosno transkateterska implantacija aortne valvule (TAVI), unaprijedio mogućnost liječenja bolesnika starije životne dobi s aortnom stenozom. Ostala važna dostignuća su mogućnost perkutanog liječenja mitralne regurgitacije (MR) (MitraClip), nefarmakološka terapija za sprječavanje cerebralne embolizacije u bolesnika s fibrilacijom atrija (FA), kao što je zatvaranje aurikule lijevog atrija (LAA) i zatvaranje otvorenog foramena ovale te renalna denervacija za liječenje rezistentne arterijske hipertenzije.

Zatvaranje aurikule lijevog atrija

Fibrilacija atrija je vrlo čest i vodeći uzrok moždanog udara (MU). Razvoj FA očekujemo u jedne od četiri osobe[2]. Vrlo je vjerojatno da je istinska prevalencija podcijenjena, jer je teže otkriti paroksizmalne FA. Pacijenti s paroksizmalnim FA vjerojatno imaju sličan rizik od MU kao i pacijenti s perzistentnom FA[3].

Oralna antikoagulantna terapija je oduvijek bila prva linija liječenja za sprečavanje MU, ali sa sobom nosi značajne rizike. Uski terapijski prozor varfarina zahtjeva osjetljivu ravnotežu između nedostatne učinkovitosti i znatno povišenog rizika od krvarenja, stoga se potrebne učestale laboratorijske kontrole. Također, postoje i brojne interakcije s hranom i lijekovima koje imaju veliki utjecaj na svakodnevni život bolesnika. Do 40% bolesnika s FA imaju kontraindikacije za antikoagulantnu terapiju. Čak i uvjetima kliničkih istraživanja, značajan dio bolesnika je ispod ili iznad terapijskih vrijednosti kod uzimanja varfarina. U studiji provedenoj kod 41.900 bolesnika s kroničnom FA, samo 70% bolesnika liječenih varfarinom je nastavilo uzimati ovu terapiju u razdoblju od godinu dana, što dodatno naglašava probleme antikoagulantne terapije.

Među pacijentima s nevalvularnom FA, velika većina tromba nastaje u aurikuli lijevog atrija (LAA). Područje LAA predstavlja slijepi završetak u kojem se stvaraju uvjeti za zastoj krvi i stvaranje tromba. Stoga bi se moglo očekivati da bi izdvajanje LAA iz cirkulacije moglo smanjiti rizik od MU. Razvijeno je nekoliko metoda — kirurška ligacija ili amputacija i okluzija perkutanim kateterom s posebnim okluzijskim uređajima (**Slika 1**).

options for aortic valve stenosis, transcatheter aortic valve implantation (TAVI) has improved the treatment options for elderly patients with aortic valve stenosis. Other important developments are the percutaneous treatment options for mitral regurgitation (MR) (MitraClip), nonpharmacologic therapy to prevent cerebral embolisation in patients with atrial fibrillation (AF) such as left atrial appendage (LAA) closure and closure of the patent foramen ovale, and renal denervation to treat resistant hypertension.

Left atrial appendage closure

AF is very prevalent and the main cause of stroke. The lifetime risk of developing AF is approximately 1 in 4.[2] It is likely that the true prevalence is underestimated, because it can be difficult to detect paroxysmal AF. Patients with paroxysmal AF probably have a risk of stroke that is similar to patients with persistent AF.[3]

Oral anticoagulation has always been the first line treatment to prevent stroke, but it comes with considerable risks. The narrow therapeutic window of warfarin forces a delicate balance between lack of efficacy and a significantly elevated risk of bleeding, therefore requiring frequent blood tests. Additionally, numerous food and drug interactions exist which have a major impact on the patient's daily life. Up to 40% of patients with AF have contraindications to anticoagulation therapy. Even in trial settings, a relevant proportion of patients are either sub- or supratherapeutic on warfarin. In a study of 41,900 patients with chronic AF, only 70% of patients treated with warfarin remained on this therapy at 1 year, further highlighting difficulties with anticoagulation.

Among patients with non-valvular AF, the vast majority of thrombi evolve from the LAA. The fibrillating LAA is a cul-de-sac that creates a milieu for blood stasis and thrombus formation. Therefore, one could expect that exclusion of the LAA from the circulation could reduce the risk for stroke. Several methods have been developed-surgical ligation or amputation and percutaneous catheter based occlusion with specific occlude devices (**Figure 1**).

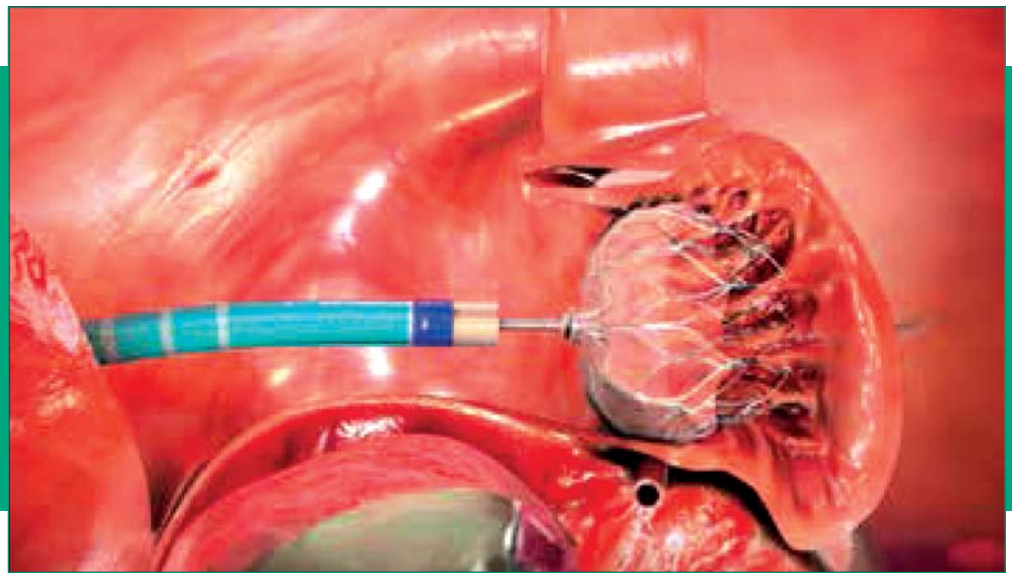

Figure 1. *Left atrial appendage occluder device.*

Kirurška ligacija ili amputacija se koristi već mnogo godina iako postoji vrlo malo dokaza o njezinoj učinkovitosti.[5] Naravno, izvodi se samo kao usputni zahvat kod primjerice operacije zalistaka, ali ne kao samostalni postupak.[6]

Perkutane metode se razvijaju od 2002. godine. Dovršene su preliminarne studije dva sustava posebno izrađena za tu svrhu (Percutaneous LAA Transcatheter Occlusion (PLAATO) i Watchman).[7] Ovi uređaji se postavljaju venskim putem i transseptalnim prolazom u lijevi atrij (LA). Obilježeni su oznakom CE (usklađeni s europskim standardima) u Europi, ali još nisu odobreni od strane Američke agencije za hranu i lijekove (FDA) za kliničku uporabu.

Osim ova dva, također su dostupni i sustavi Amplatzer kardijalni čep i Lariat sustav (omča).

PLAATO sustav

PLAATO sustav je naprava koja se postavljala u LAA putem transseptalnog katetera. Imala je samoširući nitinolski okvir koji je bio pokriven materijalom nepropusnim za krv, čime se zatvara aurikula i sprječava stvaranje ili izbacivanje tromba. Međutim, tijekom praćenja bilo je komplikacija, perikardijalni izljev kod osam bolesnika, dva MU, dvije tranzitorne ishemijske atake i tri smrtna slučaja nevezana uz proceduru.[8] Proizvođač je prekinuo razvoj PLAATO sustava.

Watchman sustav

Watchman sustav je također šireća naprava, koja se postavlja u LAA putem transseptalnog katetera. Implantirana naprava je građena od samoširećeg nitinolskog okvira koji ga učvrsti u LAA. Za razliku od PLAATO, materijal korišten kod Watchman sustava propušta krv.[9] Iz tog razloga kod bolesnika je neophodna uobičajena tromboembolijska profilaksa varfarinom dok uređaj ne endotelizira (npr. najmanje 45 dana nakon implantacije), kada se transoezofagijskim ultrazvukom srca potvrdi endotelizacija. Osim toga, svi bolesnici moraju uzimati acetilsalicilatnu kiselinu (81-325 mg) i klopidogrel (75 mg) dnevno tijekom 6 mjeseci.

Watchman sustav je ispitivan u studiji PROTECT AF u kojem je više od 700 bolesnika s nevalvularnom FA bilo randomizirano u omjeru 2:1 bilo za uređaj (s gore navedenom antikoagulantnom i antiagregacijskom terapijom) ili dugoročnu upotrebu varfarina (vrijednost INR 2.0 do 3.0).[10] Bila je dizajnirana kao studija neinferiornosti. Kriteriji za uključivanje su bili bolesnici s paroksizmalnom, perzistentninom ili permanentnom FA i svi su bolesnici imali bodove po ljestvici CHADS2 ≥1.

Istraživanjem se potvrdila neinferiornost zatvaranja aurikule s Watchman uređajem u odnosu na terapiju varfarinom razmatrajući primarne zajedničke ishode, koji su sastojali od MU, sistemske embolije i kardiovaskularne smrti s rizikom omjera 0.62 (95% CI 0.35-1.25).[11] Međutim, primarni zajednički ishodi sigurnosti liječenja (koji se sastoje od velikih krvarenja, perikardijalnog izljeva, MU povezanog s postupkom i embolizacija uređaja) bili su povećani u skupini s uređajem (7,4 u odnosu na 4,4 događaja na 100 bolesnika po godini). Većina nepovoljnih događaja u skupini s uređajem dogodilo se rano nakon zahvata. Od ukupnog broja oko 50% su bili perikardijalni izljevi koji su zahtijevali drenažu.

Dva kasnije vođena registra su pokazala poboljšanje sigurnosti ovog uređaja, vjerojatno zbog efekta krivulje učenja. Učestalost komplikacija unutar prvih 7 dana iznosila je 3,7 %

Surgical ligation or amputation has been used for many years even though there is very little evidence regarding its effectiveness.[5] Of course, it is only performed as a 'bystander' operation in the case of, for example, valve surgery, not as a stand alone procedure.[6]

Percutaneous methods have been developed since 2002. Preliminary studies of two systems specifically designed for this purpose (Percutaneous LAA Transcatheter Occlusion (PLAATO) and Watchman systems) have been completed.[7] These devices are deployed via a venous access and transseptal crossing into the left atrium (LA). These devices are CE (European Conformity) marked in Europe but are not approved by the US Food and Drug Administration (FDA) for clinical use yet.

In addition to these two systems, the Amplatzer cardiac plug and the Lariat (snare device) system are also available.

PLAATO system

The PLAATO system was a device that was placed in the LAA via a transseptal catheter. It had a self- expanding nitinol frame that was covered by a fabric that was impermeable to blood, thus sealing the LAA and preventing thrombus formation or dislodgement. However, there were adverse effects during follow-up-for example, pericardial effusion in eight patients, two strokes, two transient ischaemic attacks, and three non-procedural deaths.[8] The manufacturer has discontinued development of the PLAATO device.

Watchman device

The Watchman device also involves an expandable device deployed in the LAA via a transseptal catheter. The implanted device has a self-expanding nitinol frame to secure it in the LAA. Unlike the PLAATO device, the fabric of the Watchman device is permeable to blood.[9] For this reason, patients require conventional thromboembolic prophylaxis with warfarin until the device is endothelialised (eg, at least 45 days post-implant), at which time transoesophageal echocardiography is performed to ensure endothelialisation. In addition, all patients are treated with both aspirin (81-325 mg) and clopidogrel (75 mg) daily for 6 months.

The Watchman device was evaluated in the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with AF) trial in which over 700 patients with non-valvular AF were randomly assigned in a 2 : 1 ratio to either the device (with the above antithrombotic regimen) or to long term warfarin (international normalised ratio 2.0 to 3.0).[10] It had a non-inferiority design. Inclusion criteria allowed for patients with paroxysmal, persistent, or permanent AF and all patients had a CHADS2 score ≥1.

The trial confirmed non-inferiority of Watchman atrial appendage occlusion compared to warfarin therapy regarding the primary end point, a composite of stroke, systemic embolism, and cardiovascular death with a risk ratio of 0.62 (95% CI 0.35 to 1.25).[11] However, the primary safety end point (composite of major bleeding, pericardial effusion, procedure related stroke, and device embolisation) was increased in the device group (7.4 vs 4.4 events per 100 patient-years, respectively). Most of the events in the device group occurred early. Of these, about 50% were pericardial effusions requiring drainage.

Two later registries showed improving safety of this device, probably due to a learning curve effect. The rate of compli-

u odnosu na 7,7% u početnom randomiziranom istraživanju.[11,12]

Amplatzer septalni zatvarač i Amplatzer kardijalni čep

Amplatzer septalni zatvarač koristi jednostavniju tehniku nego što je to PLAATO tehnika. Umjesto opće anestezije koja se koristila u PLAATO postupku, često se implantira u lokalnoj anesteziji. Serija slučajeva koja je uključivala 16 bolesnika je prikazala način korištenja Amplatzer septalnog zatvarača za zatvaranje LAA u lokalnoj anesteziji, bez ehokardigrafskog vođenja.[13] Amplatzer kardijalni čep je drugi uređaj izrađen posebno za zatvaranje LAA i u fazi je kliničkih ispitivanja.[14] Ovaj uređaj se bazira na nitinolu i sastoji se od lijevog atrijskog diska i distalnog čepa spojenog na lijevi atrijski disk kratkim strukom. Distalni čep sadrži šest pari kukica kreiranih u svrhu bolje fiksacije unutar aurikule. Ovaj je uređaj kraći od Watchman sustava, a može biti primjenjiviji kod osoba s izmjenjenom morfologijom aurikule. Podaci na životinjama su objavljeni i pokazali su jednostavno postavljanje uređaja s potpunim zatvaranjem aurikule 30. dana i 90. dana praćenja.[14,15]

Buduća uloga ovog postupka također će ovisiti o drugim alternativama terapiji varfarinom, kao što su novi antikoagulansi. Za sada ne postoji jak dokaz koji upućuje na to da su superiorniji u odnosu na varfarin, osim rivaroksabana koji je pokazao manji rizik od krvarenja, ali su obećavajuća alternativa varfarinu i puno ih je jednostavnije koristiti.[16]

Ažurirane ciljne smjernice Europskog kardiološkog društva (ESC) iz 2012. god. za zbrinjavanje FA donose slabu preporuku za korištenje intervencijskog, perkutanog zatvaranja LAA u bolesnika s visokim rizikom MU i kontraindikacijom za dugoročnu antikoagulaciju.[17] Zaključno perkutano zatvaranje LAA se čini jednako učinkovitim kao varfarin prema jednom randomiziranom istraživanju, ali se događaju periproceduralne komplikacije (kao što je perikardijalni izljev).

Zatvaranje aurikule lijevoga atrija — Ključne točke:

• Perkutano zatvaranje LAA predstavlja obećavajuću alternativu terapije s varfarinom kod bolesnika sa FA koji imaju visok rizik MU.

• Podaci su oskudni, a postupak bi trebalo ograničiti na bolesnike koji imaju jasne kontraindikacije za varfarin.

• Novi antikoagulansi (npr. rivaroksaban) predstavljaju još jednu alternativu za bolesnike s kontraindikacijoma za varfarin.

Intervencije na mitralnom zalisku

Prevalencija umjerene ili teške MR je veća od 10% u starijih od 75 godina, a prirodni tijek bolesti je često fatalan.[18] Međutim, bolesnici s teškom kroničnom MR često imaju ostale komorbiditete koji povećavaju rizik za operacije srca. Postoji žurna potreba za manje invazivnim, perkutanim načinom liječenja. Ispitivano je nekoliko postupaka. Trenutno, najviše obećava MitraClip sustav (Abbott Laboratories, Abbott Park, Illinois, SAD). On se temelji na kirurškoj tehnici Alfieri stich, rekonstrukcija edge-to-edge (**Slika 2**).[19]

MitraClip sustav se sastoji od katetera kroz koji se plasira "kvačica" te sustava uvođenja "kvačice" koji uključuje odvojivu "kvačicu" s dakronskim pokrovom koji omogućuje urastanje tkiva. Sustav uvođenja "kvačice" sadrži i kontrolni mehanizam za otvaranje i zatvaranje dva kraka "kvačice". Tkivo mitralnog listića se drži između krakova obje strane hvatalj-

cations within 7 days were 3.7% as compared to 7.7% in the initial randomised trial.[11,12]

Amplatzer septal occluder and Amplatzer cardiac plug

The Amplatzer septal occluder uses a simpler technique than the PLAATO technique. Instead of general anaesthesia as used in the PLAATO procedure, it is often implanted under local anaesthesia. A case series involving 16 patients demonstrated the use of the Amplatzer septal occluder to close LAA under local anaesthesia without echocardiographic guidance.[13] The Amplatzer cardiac plug is another device designed specifically for closure of the LAA and is undergoing clinical trials.[14] This device is nitinol based and consists of a left atrial disk and a distal plug connected to the left atrial disk by a short waist. The distal plug contains six pairs of barbs designed to increase stability within the appendage. This device is shorter than the Watchman device and may be more advantageous in individuals with the variable morphology of the appendage. Animal data have been published demonstrating uncomplicated device delivery with complete occlusion of the appendage at 30-day and 90-day follow-ups.[14,15]

The future role of this procedure will also depend on other alternatives to warfarin therapy, such as the novel anticoagulants. So far, there is no strong evidence suggesting they are superior to warfarin, apart from rivaroxaban which showed a lower bleeding risk, but they are a promising alternative to warfarin and much easier to use.[16]

The 2012 focused update of the European Society of Cardiology (ESC) guidelines for the management of AF makes a weak recommendation for the use of interventional, percutaneous LAA closure in patients with a high stroke risk and contraindications for long term anticoagulation.17 In conclusion, percutaneous LAA closure seems as effective as warfarin according to one randomised trial, but comes with periprocedural complications (such as pericardial effusion).

Left atrial appendage closure — Key points:

• Percutaneous LAA closure is a promising alternative to warfarin therapy in patients with AF who have a high stroke risk.

• Data are scarce and the procedure should be limited to patients who have clear contraindications for warfarin.

• Novel anticoagulants (eg, rivaroxaban) represent another alternative for patients with a contraindication for warfarin.

Mitral valve interventions

The prevalence of moderate or severe MR is over 10% in those older than 75 years and the natural course is often fatal.18 However, patients with chronic severe MR often have other comorbidities that increase their risk for cardiac surgery. There is an urgent need for a less invasive percutaneous approach. Several approaches have been tested. Currently, the most promising one is the MitraClip system (Abbott Laboratories, Abbott Park, Illinois, USA). It is based on the surgical Alfieri stitch technique, an edge-to-edge repair (**Figure 2**).[19]

The MitraClip system consists of a catheter to guide the path of the clip delivery and a clip delivery system which includes the detachable clip with a Dacron cover to enable tissue ingrowth. The clip delivery system has a control mechanism to open and close the two arms of the clip. Tissue of the mi-

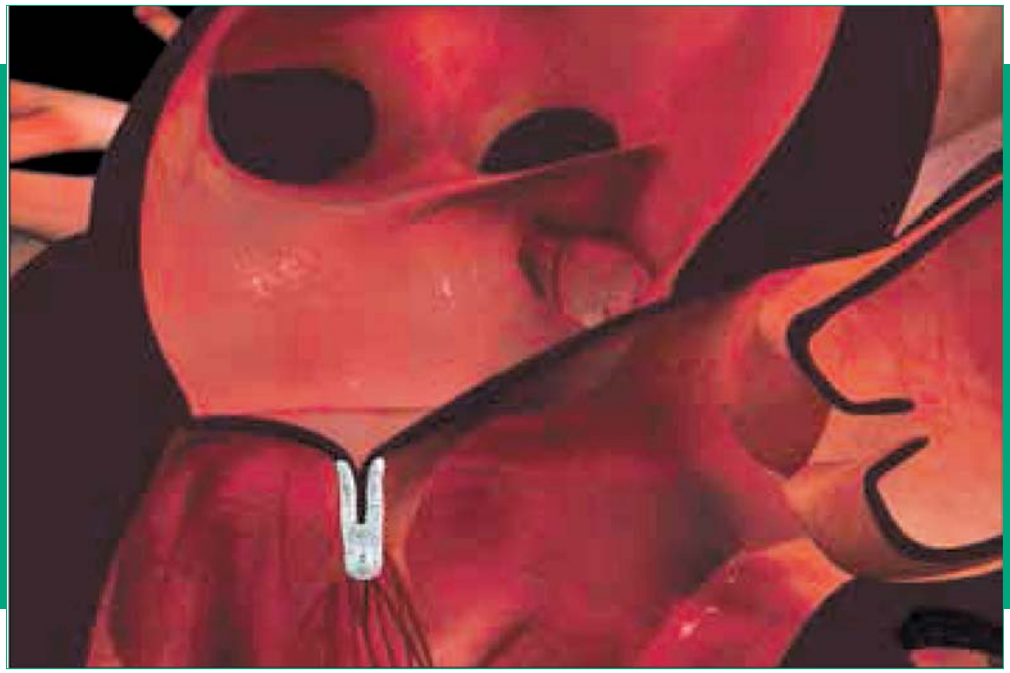

Figure 2. *MitraClip procedure.*

ke u obliku slova U. Zatim se "kvačica" zatvori i zaključa tako da dva listića ostanu spojena i rekonstruirana.

Uobičajeni postupak se radi pod općom anestezijom, vodeći kateter postavi se kroz femoralnu venu do lijevog atrija transseptalnim pristupom. Koristeći spomenuti pristup, MitraClip se uvodi i postavi. Sustav uvođenja "kvačice" podešava MitraClip s linijom koaptacije, zgrabe se listići mitralnog zalistka, a "kvačica" se djelomično zatvori na oko 60°. Idealna duljina za koaptaciju je najmanje 2 mm. Transoezofagijska ehokardiografija (TEE) se koristi za usmjeravanje postavljanja "kvačice", a kasnije radi procjene smanjenja mitralne regurgitacije. Periproceduralno praćenje ultrazvukom je ključno za ovaj postupak, kao što treba biti slučaj i za kiruršku rekonstrukciju mitralnog zalistka; mitralni zalistak je relativno složena struktura.[20] Ako se postigne adekvatno postavljanje listića na 60° zatvaranja "kvačice", nastavi se zatvaranje "kvačice" i spajanje listića i postizanja koaptacije te maksimalno smanjenje regurgitacije u bolesnika bilo s degenerativnom ili funkcionalnom mitralnom regurgitacijom. Kako bi se izbjegla stenoza nakon postavljanja MitraClipa, početna površina mitralnog zalistka treba biti >4 cm^2.

Prva klinička iskustva na ljudima sa MitralClip sustavom su praćena u I. fazi kliničkog istraživanja EVEREST.[21] Studija je uključivala 27 bolesnika. Četrnaest bolesnika je imalo smanjenje mitralne regurgitacije na ≤2+ u šest mjesečnom razdoblju. Ova studija je pokazala ohrabrujuće rezultate za liječenje mitralne insuficijencije u bolesnika koji imaju visok rizik za konvencionalne kirurške zahvate.

Središnje istraživanje EVEREST II je randomiziralo 279 bolesnika s kroničnom umjereno teško ili teškom regurgitacijom (stupanj 3+ ili 4+) na perkutanu intervenciju MitraClip sustavom ili operaciju mitralnog zalistka u omjeru 2:1.[22] Iako je prije otpusta iz bolnice perkutana terapija bila manje učinkovita u smanjenju regurgitacije, učestalost smanjenja regurgitacije nakon 12 i 24 mjeseca je bila slična u obje skupine. Međutim, utvrđeno je da je perkutana metoda sigurnija sa smanjenom učestalosti glavnih nepovoljnih događaja u razdoblju od 30 dana. Studija je pokazala postojano kliničko

tral leafiet is held between the arms and each side of the U-shaped gripper. Then, the clip is closed and locked so that the two leafiets stay approximated for repair.

Usually under general anaesthesia, the guide catheter is inserted through the femoral vein to reach the left atrium through a transseptal approach. Using this path, the MitraClip is delivered and deployed. The clip delivery system aligns the MitraClip with the line of coaptation, tissues of the mitral valve leafiet are grasped, and the clip is partially closed to about 60°. Ideal length for coaptation is at least 2 mm. Transoesophageal echocardiography (TOE) is used to guide the deployment of the clip and later to evaluate the reduction in MR. Periprocedural imaging is key for this procedure, as it should be the case for surgical mitral valve repair; the mitral valve is a relatively complex structure.[20] If there is adequate leaflet insertion at 60° of clip closure, the clip is further closed to appose the leafiets and induce coaptation to reduce MR maximally in patients with either degenerative or functional MR. In order to avoid a stenosis following placement of the MitraClip, the baseline mitral valve area should have been >4 cm^2.

The initial human clinical experience with MitraClip was studied in the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) phase I study.[21] The study included 27 patients. Fourteen of the patients had MR reduced to ≤2+ at 6 months. The study showed promise for MR patients at high risk for conventional surgical procedures.

The pivotal EVEREST II trial randomised 279 patients with chronic moderately severe or severe MR (grade 3+ or 4+) to undergo either percutaneous MitraClip or mitral valve surgery in a 2:1 ratio.[22] Although before hospital discharge percutaneous therapy was less effective at reducing MR, the rates of MR reduction at 12 and 24 months were similar in both the groups. However, percutaneous therapy was found to be safer with a reduced rate of major adverse events at 30 days. The study showed sustained clinical improvement, as assessed by quality of life, heart failure status, and left ventricular function.

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poboljšanje uzimajući u obzir i kvalitetu života, stupanj srčanog zatajivanja i funkciju lijeve klijetke.

EVEREST II studija se nije bila posebno fokusirala na vrlo rizične bolesnike. Srednja životna dob ispitanika je bila 66 godina, prosječna ejekcijska frakcija je iznosila 60%, a značajni komorbiditeti su bili rijetki. U istraživanju EVEREST II High Risk Study (HRS), bolesnici su imali tešku MR (3-4+), prosječna dob je bila 77 godina, a procijenjena kirurška stopa smrtnosti je bila ≥12%.[23] Više od 50% ovih bolesnika je već bilo podvrgnuto kardiokirurškom zahvatu. Oni su retrospektivno bili uspoređeni sa skupinom bolesnika koji su prethodno bili istodobno procjenjivani, ali nisu bili uključeni u studiju EVEREST II. Ti bolesnici su bili liječeni standardnom medikamentoznom terapijom.

Periproceduralna smrtnost do 30 dana nakon zahvata je bila slična za obje skupine (7,7% u HRS u odnosu na 8,3% u komparativnoj skupini). Preživljavanje nakon 12 mjeseci je bilo veće u HRS skupini (76% prema 55%). Kod preživjelih uspoređeni su početni i podaci nakon 12 mjeseci. Mitralna regurgitacija je smanjena na ≤2+ kod 78% bolesnika. Došlo je do smanjenja enddijastoličkog volumena lijeve klijetke (172-140 mL), endsistoličkog volumena (82-73 mL), poboljšanja prema New York Heart Association funkcionalnog stupnja (III./IV. na početku u 89% u I./II. stupanj kod 74%; p < 0,001), kvaliteti života i mentalnom statusu u razdoblju od 12 mjeseci.

Feldman i *sur.*[24] su izvijestili o kliničkim rezultatima korištenja "kvačice" u kohorti od 107 bolesnika praćenih 3 godine. Sačinjavalo ju je 55 bolesnika liječenih tijekom istraživanja izvedivosti EVEREST faze I i 52 bolesnika uključena i liječena u glavnoj studiji EVEREST II, što predstavlja prerandomizirano početno iskustvo. Od ukupno uspješno liječenih bolesnika, 66% je postiglo primarni zajednički ishod, koji sadrži preživljenje, potrebu za operacijom mitralnog zalistka ili MR >2+ u razdoblju od 12 mjeseci, a kod većine bolesnika čak i u razdoblju od 3 godine.

Uređaj MitraClip je dobio CE odobrenje i već se koristi kod tisuće bolesnika diljem svijeta.[25,26] Dok se ne ishodi odobrenje od FDA, "kvačica" je dostupna u SAD samo sudjelovanjem u REALISM registru otvorenog tipa. Pacijenti uključeni u ovaj klinički registar uvršteni su u skupinu visokorizičnih ili skupinu bolesnika bez visokog rizika. Praćeni su u razdoblju od 30 dana, 6 mjeseci i 12 mjeseci.

Privremeni rezultati studije EVEREST II REALISM predstavljeni su na znanstvenim skupovima Društva za kardiovaskularnu angiografiju i intervencije (SCAI) 2011.[27-29] Prosječna životna dob bolesnika u registru bila je iznad 70 godina. Uređaj MitraClip je bio siguran, a učestalost smrtnih ishoda nakon 30 dana iznosila je 3.8%.[28] Nakon 1. godine 83% visokorizičnih bolesnika je imalo samo blagu do umjerenu MR (1+ ili 2+). Prije postupka, ocjena kvalitete života je bila lošija za bolesnike s funkcionalnom regurgitacijom nego za one sa degenerativnom regurgitacijom,[29] ali je također u toj skupini došlo i izraženijeg poboljšanja nakon postupka.

Analiza prvih 100 bolesnika u švicarskom MitraSwiss registru je pokazala da su kongestivno zatajivanje srca i prethodna operacija premoštenja koronarnih arterija (CABG) prije implantacije bili prediktori lošeg ishoda s MitraClip sustavom.[26] Smanjenje MR na ≤2+ tijekom postupka i niski stupanj MR kod otpusta su bili prediktori boljeg srednjoročnog preživljavanja. Gaemperli *i sur.*[30] su dokazali poboljšanje u hemodinamskom profilu odmah nakon postupka. Ovo akutno hemodinamsko poboljšanje je bilo povezano i s povoljnim srednjoročnim ishodom.

The EVEREST II study was not specifically focused on very high risk patients. The mean age was 66 years, mean ejection fraction was 60%, and major comorbidities were rare. In the EVEREST II High Risk Study (HRS), however, patients had severe MR (3-4+), a mean age of 77 years, and an estimated surgical mortality rate of ≥12%.[23] More than 50% of these patients had undergone previous cardiac surgery. They were compared retrospectively with a group of patients who were screened concurrently but not enrolled into the EVEREST II study. These patients had been treated by standard medical therapy.

The 30-day procedure related mortality rate was similar in both the groups (7.7% in the HRS vs 8.3% in the comparator group). The 12-month survival was higher in the HRS group (76% vs 55%). In surviving patients the baseline and 12-month data were compared. MR grade had reduced to ≤2+ in 78% patients. There was improvement in left ventricular end-diastolic volume (172-140 mL), end-systolic volume (82-73 mL), New York Heart Association functional class (III/IV at baseline in 89% to class I/II in 74%; p < 0.001), quality of life and mental component score at 12 months.

Feldman *et al*[24] reported clinical results of use of the clip in a cohort of the first 107 patients followed for as long as 3 years. These were 55 patients treated in the EVEREST phase I feasibility trial, and 52 roll-in patients treated in the EVEREST II pivotal trial representing the pre-randomisation start-up experience. Out of the successfully treated patients, 66% achieved the primary end point of freedom from death, mitral valve surgery, or MR >2+ at 12 months. There was sustained freedom from death, surgery or recurrent MR in most patients even at 3 years.

The MitraClip device has received a CE approval and has already been used in thousands of patients worldwide.[25,26] Until approval is obtained from the FDA, the clip is available only through the REALISM continued access registry in the USA. Patients enrolled into this 'real-world' registry are assigned to either the high risk arm or the non-high risk arm. They are followed up at 30 days, 6 months, and 12 months.

Interim results of the EVEREST II REALISM study were presented at the Society for Cardiovascular Angiography and Interventions (SCAI) 2011 scientific sessions.[27-29] On average, the age of patients in the registry was over 70 years. The MitraClip procedure was safe with a 30-day mortality of 3.8%.[28] At 1 year, 83% of patients in the high risk group had only mild to moderate MR (1+ or 2+). Before the procedure, the quality of life scores were worse for functional MR than for degenerative MR,[29] but there was also greater improvement after the procedure.

An analysis of the first 100 patients in the MitraSwiss register from Switzerland showed that congestive heart failure before clip implantation and previous coronary artery bypass grafting (CABG) were predictors of poor outcome with the MitraClip procedure.[26] A reduction of MR to ≤2+ during the procedure and a low grade MR at discharge predicted better mid-term survival. Gaemperli *et al*[30] documented an improvement in the haemodynamic profile immediately after the procedure. This acute haemodynamic improvement was associated with favourable mid-term outcome.

In conclusion, the MitraClip implantation is inferior to surgical mitral repair for reducing MR grade, but it is probably safer in higher risk patients. Even though the reduction in MR is less than with surgery, the subjective symptom improvement is comparable. The most suitable patients are those

Zaključno, implantacija MitraClip sustava je inferiorna kirurškoj mitralnoj rekonstrukciji za smanjenje stupnja mitralne regurgitacije, ali je vjerojatno sigurnija za visokorizične bolesnike. Iako je smanjenje MR manje nego kod operacije, subjektivno poboljšanje simptoma je usporedivo. Većina pogodnih bolesnika su oni koji imaju visoki rizik od operacije i posebno oni s funkcionalnom MR. Optimalni trenutak za postupak nije jasan, ali za bolesnike koji se podvrgavaju operaciji podaci ukazuju da je bolje da se ona obavi čim prije.[31] To ima smisla jer je kirurgija postala sigurnija i došlo je do promjene u razmatranju odnosa rizika i dobrobiti postupka. Budući da je perkutani pristup još dodatno smanjio periproceduralni rizik, isto razmatranje bi se i ovdje trebalo primijeniti.

Intervencije mitralnog zaliska — Ključne točke:

• Podaci za postupak sa uređajem MitraClip su vrlo ograničeni i potječu uglavnom iz studije EVEREST II.

• Iako studija EVEREST nije uključila visokorizične bolesnike, ovaj postupak bi se trebao ograničiti na one s visokim rizikom od kirurške operacije zbog ograničenog učinka.

Intervencije na aortnom zalisku

Stenoza aortnog zalistka (AS) je vrlo česta bolest, sa stalnim porastom prevalencije u starijoj životnoj dobi.[32,33] Kod pravilno odabranih bolesnika, zamjenom aortnog zalistka (AVR) se bitno poboljšavaju simptomi i produžuje životni vijek. No, kod bolesnika sa značajnim komorbiditetima, kao što je često slučaj u ovoj skupini starijih bolesnika, operacija AVR ne mora biti primjerena zbog rizika kojeg nosi. Manje invazivna metoda je perkutana aortna valvuloplastika, ali ona ima ograničeni i obično samo privremeni učinak. Transkateterska zamjena aortnog zalistka (TAVR ili TAVI) pruža alternativu za liječenje AS u bolesnika s visokim rizikom od kirurškog zahvata. Također je metoda izbora i u bolesnika kod kojih postoje tehnički otežavajući faktori za operaciju, primjerice, "porculanska" aorta ili prethodno zračenje medijastinuma ili jake postoperativne priraslice ili prethodna infekcija sternuma sa složenom rekonstrukcijom ili otvorena funkcionalna LIMA premosnica.

Najnovije Europske smjernice iz 2012. navode da se TAVR preporuča bolesnicima s teškom simptomatskom AS, koji se, prema nalazu lokalnog multidisciplinarnog tima za bolesti srca, smatraju neprikladnim za konvencionalni kirurški zahvat zbog teških komorbiditeta. Među visokorizičnim bolesnicima koji su potencijalni kandidati za operaciju, odluka se mora donositi pojedinačno i istu mora usaglasiti tim za bolesti srca. Procjene rizika mogu biti od pomoći za kliničko odlučivanje. Logistički EuroSCORE ≥20% vrlo je etabliran i često se koristi i u ovoj indikaciji; ocjena ≥20% je predložena za definiranje visokog rizika. Međutim, njime se općenito precjenjuje operativni mortalitet. Čimbenici kao što su to plućna hipertenzija ili disfunkcija desne klijetke nisu razmatrani. Noviji EuroScore II je vjerojatno više koristan; alternativno, se može koristiti ljestvica Društva torakalnih kirurga (STS) s ocjenom ≥10% koja ukazuje na visok rizik (prag ≥8% je korišten u istraživanju PARTNER). Moramo biti svjesni da još nije utvrđena 'savršena' procjena rizika za TAVI bolesnike; one su razvijene za bolesnike koji se podvrgavaju operaciji srca uglavnom CABG. Ove procjene rizika ne uzimaju u obzir čimbenike koji su važni kada se raspravlja o TAVR u odnosu na kirurški AVR, kao što su ukupno psihofizičko stanje, porculanska aorta, prethodno zračenje prsnog koša ili otvorene funkcionalne aortokoronarne premosnice. Dakle, konačna odluka trebala bi se temeljiti na sveobuhvatnoj kliničkoj prosudbi. Važno je znati da se TAVI trenutno ne

at high risk for surgery and particularly those with functional MR. The optimal time point for the procedure is not clear, but for patients undergoing surgery the data indicate that sooner is probably better.[31] This makes sense, as surgery has become safer and has changed the risk-benefit considerations. Since the percutaneous approach has further reduced the periprocedural risk, the same consideration should apply here as well.

Mitral valve interventions — Key points:

• Data for the MitraClip system procedure are very limited and derive mainly from the EVEREST II trial.

• Even though the EVEREST trial did not enrol very high risk patients, the procedure should be limited to those at high surgical risk because of the limited effect.

Aortic valve interventions

Aortic valve stenosis (AS) is a very common disease, with increasing prevalence at older age.[32,33] In properly selected patients, aortic valve replacement (AVR) substantially improves symptoms and increases life expectancy. However, for patients with major comorbidities, as is often the case in this elderly patient group, AVR surgery may not be appropriate because of the risks involved. A less invasive means is percutaneous aortic valvuloplasty, but this has a limited and usually only a temporary effect. Transcatheter aortic valve replacement (TAVR or TAVI) provides an alternative for treating AS in patients at high surgical risk. It is also a preferred option in patients who may have technical issues with surgery-for example, porcelain aorta or prior mediastinal radiation, or surgery with dense adhesions, or prior sternal infection with complex reconstruction, or a patent left internal mammary graft.

The most recent 2012 European guidelines state that TAVR is recommended in patients with severe symptomatic AS who are, according to the local 'heart team' (multidisciplinary team), considered unsuitable for conventional surgery because of severe comorbidities. Among high risk patients who are potential candidates for surgery, the decision should be individualised and discussed in a 'heart team'. Risk scores can be helpful for the clinical decision making. The logistic EuroSCORE ≥20% is very established and often used in this setting as well; a score ≥20% has been proposed to define high risk. However, it generally overestimates operative mortality. Factors such as pulmonary hypertension or right ventricular dysfunction are not accounted for. The newer EuroScore II is probably more useful; alternatively, the Society of Thoracic Surgeons (STS) score can be used with a score ≥10% indicating high risk (a threshold of ≥8% was used in the PARTNER A trial). We have to be aware that no 'perfect' TAVI risk score has been established yet; they have been developed for patients undergoing cardiac surgery, predominantly CABG. These scores do not consider factors which are important when debating TAVR versus surgical AVR, such as frailty, porcelain aorta, history of chest radiation or patent coronary bypass grafts. Therefore, the final decision should be based on a comprehensive clinical judgement. Importantly, TAVI should currently not be performed in patients at intermediate surgical risk until more data for this group of patients are available, for example, from the ongoing SURTAVI (Surgery and Transcatheter Aortic Valve Implantation) trial (NCT01586910).[34]

treba izvoditi u bolesnika sa srednjim rizikom od kirurškog zahvata dok ne bude dostupno više podataka za ovu skupinu bolesnika, primjerice podaci trenutnog istraživanja SURTAVI (Kirurška i transkateterska implantacija aortalne valvule) (NCT01586910).[34]

Smjernice American College of Cardiology (ACC) iz 2012. su vrlo slične i jednako podržavaju odluku multidisciplinarnog tima za bolesnike s visokim rizikom za operacije, definirajući "previsoki rizik za operaciju" kao procijenjeni pojavu ≥50% rizik od smrti ili ireverzibilnog morbiditeta u prvih 30 dana.[35] Iako su ove smjernice novijeg datuma, s rastućim iskustvom indikacija za TAVR se brzo širi u nekim zemljama. U odabranim centrima u Njemačkoj, TAVR predstavlja više od jedne trećine svih AVR postupaka. TAVR je najjeftinije učinkovito liječenje za one koji se ne mogu podvrći operaciji AVR.36 U SAD-u je uvođenje TAVR-a bilo nešto sporije uglavnom zbog regulatornih razloga.[35-37] Zanimljivo je da je u većini centara uvođenje TAVI bilo povezano i s povećanjem konvencionalne kirurške AVR aktivnosti.[38,39] Trenutno su dva zalistka u širokoj uporabi i imaju odobrenje FDA — Edwards Sapien balon koji proširuje transkatetersku srčanu valvulu (THV) (Edwards Lifesciences, Irvine, California, SAD) samoproširiv CoreValve (Medtronic Inc, Minneapolis, Minnesota, Sjedinjene Američke Države).

Vodeća studija za TAVR, u istraživanju PARTNER primjenjena je Edwards Sapien valvula. Rezultati iz registra SOURCE donose rezultate primjene Edwards Sapien valvule kod uzastopnih bolesnika iz Europe, s učestalosti uspjeha ovog zahvata od 93,8% i niskom pojavnošću komplikacija povezanih s zahvatom.[40] Pojavnost MU je bila slična (2,5%) kod transfemoralnog i transapikalnog pristupa. Smrtnost nakon 30 dana je bila niža (6,3% u odnosu na 10,3%) i jednogodišnje preživljavanje je bilo više (81,1% naspram 72,1%) u bolesnika s transfemoralnim pristupom.[40,41] No, učestalost vaskularnih komplikacija s transfemoralnim TAVR je bila znatno viša (22,9% u odnosu na 4,7%), vjerojatno zbog velikog promjera femoralne uvodnice.

Većina timova koji primjenjuje TAVR preferira transfemoralni pristup jer se time izbjegava kirurški zahvat na prsištu i smanjuje se postoperativna bol.[42] Osim toga to je najmanje invazivna metoda.[43] No, torakalna epiduralna anelgezija koja se primjenjuje tijekom transapikalnog TAVR može značajno smanjiti bol i periproceduralne respiratorne komplikacije.[44]

Edwards Sapien XT transkateterska valvula ima okvir od kobalt kroma s građom mrežice koja je tanja i ima otvoreniju strukturu.[45] Istraživanje kod 120 bolesnika je pokazalo da je postignut kratkoročni učinak kao i s prethodnom SAPIEN valvulom, ali je bila povezano s tri puta manjim rizikom od velikih vaskularnih komplikacija.[46]

Istraživanje PARTNER je bila prva prospektivna randomizirana kontrolirana studija za TAVR u svijetu. Bile su formirane su dvije skupine:

• PARTNER A randomizirao je 699 visokorizičnih bolesnika na TAVR ili operativnu AVR:

• PARTNER B randomizirao je 358 neoperabilnih bolesnika na TAVR ili standardnu farmakološku terapiju.

Smrtnost nakon 30 dana je bila viša kod TAVR bolesnika nego u liječenih standardnom farmakološkom terapijom (5% : 2,8%, p=0.41), ali manje za TAVR nego onih koji su se podvrgli otvorenom kirurškom zahvatu (3,4% : 6,5%, p=0.07).[47]

U kohorti PARTNER A, kod TAVR skupine bilo je više velikih MU (3,8% : 2,1% u 30 dana; 5,1% : 2,4% u 1. god.) i većih vaskularnih komplikacija (11,0% : 3,2% u 30 dana; 11,3% : 3,5% u 1. god.). Kod skupine s kirurškim AVR bio je veći

The 2012 American College of Cardiology (ACC) guidelines are very similar and equally endorse a multidisciplinary team decision for patients at high risk for surgery, defining 'too high risk for surgery' as an estimated ≥50% risk of death or irreversible morbidity at 30 days.[35] Even though these guidelines are very recent, with increasing experience the indication for TAVR is rapidly expanding in some countries. In selected centres in Germany, TAVR accounts for over one-third of all AVR procedures. TAVR is a cost effective treatment for those who are not eligible for surgical AVR.36 In the USA, the introduction of TAVR has been somewhat slower, mainly due to regulatory reasons.[35-37] Interestingly, in most centres, the introduction of TAVI has been associated with increase in conventional surgical AVR activity also.[38,39] Currently, two valves are in widespread use and have FDA approval-the balloon expanding Edwards Sapien transcatheter valve (THV) (Edwards Lifesciences, Irvine, California, USA) and the self-expanding CoreValve (Medtronic Inc, Minneapolis, Minnesota, USA).

The landmark trials for TAVR, the PARTNER (Placement of Aortic Transcatheter Valve) trials, have been performed with the Edwards Sapien valve. The subsequent Sapien Aortic Bioprosthesis European Outcome (SOURCE) Registry assessed results of the use of the Edwards Sapien valve in consecutive patients in Europe, with procedural success rates as high as 93.8% and a low incidence of procedure related complications.[40] Incidence of stroke was similar (2.5%) with both the transfe moral and the transapical approaches. The 30-day mortality was lower (6.3% vs 10.3%) and 1-year survival was higher (81.1% vs 72.1%) in patients with the transfemoral approach.[40,41] However, there was a much higher rate of vascular complications with transfemoral TAVR (22.9% vs 4.7%), probably because of the larger diameter of the delivery sheath.

Most TAVR teams prefer the transfemoral approach as it avoids surgical manipulation of the chest and reduces postoperative pain.[42] It is also the least invasive method.[43] However, thoracic epidural analgesia provided during transapical TAVR can significantly reduce pain and periprocedural respiratory complications.[44]

The Edwards Sapien XT valve has a cobalt chromium frame with struts that are thinner and have a more open structure.[45] A trial on 120 patients showed that it had the same short term performance as the earlier SAPIEN valve but was associated with threefold lower risk of major vascular complications.[46]

The PARTNER valve trial was the world's first prospective randomised controlled trial for TAVR. It was designed with two arms:

• PARTNER A randomised 699 high surgical risk patients to either TAVR or surgical AVR:

• PARTNER B randomised 358 inoperable patients to either TAVR or standard medical care.

The 30-day mortality was higher in TAVR patients than in those administered standard medical care (5% vs 2.8%, p=0.41) but was less for TAVR than in those undergoing open surgical AVR (3.4% vs 6.5%, p=0.07).[47]

In the PARTNER A cohort, those who underwent TAVR had a higher incidence of major strokes (3.8% vs 2.1% at 30 days; 5.1% vs 2.4% at 1 year) and major vascular complications (11.0% vs 3.2% at 30 days; 11.3% vs 3.5% at 1 year). Those treated with surgical AVR had a higher incidence of

postotak velikih krvarenja (19,5% : 9,3% u 30 dana; 25,7% : 14,7% u 1. god.) i novonastalih fibrilacija atrija (16,0% : 8,6% u 30 dana; 17,1% : 12,1% u 1. god.).

Oba postupka (kirurška AVR i TAVR) postigli su smanjenje gradijenata tlaka nad aortnim zalistkom i povećanje efektivne površine ušća (EOA) ($p<0.0001$) što se zadržalo nepromijenjeno tijekom razdoblja od dvije godine. Postupak TAVR je bio povezan s višim indeksom EOA, manjom nepodudarnosti proteze i bolesnika i većom aortnom regurgitacijom (AR).[48]

Iako je funkcija desne klijetke smanjenja nakon kirurškog postupka AVR, nema takvog učinka s TAVR.[49,50]

Novija studija je pokazala da postoji prolazna sistolička i dijastolička disfunkcija u prvih 24 h nakon uspješnog TAVR.[51] To je povezano s porastom serumskih markera ozljede miokarda i disfunkcijom i ukazuje da je postproceduralna disfunkcija nastala zbog "omamljenosti" miokarda i periproceduralne ozljede miokarda.

Postproceduralni paravulvarna AR je češća nakon TAVR nego nakon operacije.[52,53] Iz podataka studije PARTNER smo saznali, a potvrđeno je kasnijim studijama, da nema povezanosti između post-TAVR paravalvularnog propuštanja i povećanog mortaliteta. Na temelju rezultata njemačkog TAVR registra pojava značajne, angiografski ocijenjene AR neposredno nakon TAVR iznosila je 17,2%. U toj populaciji bilo je 84% sa Medtronic CoreValve zalistkom i 16% sa zaliskom Edwards Sapien. Rizik bolničkog mortaliteta je bio povećan oko 2,5 puta u bolesnika sa značajnim AR.[52] No, nejasno je da li je AR uzrok mortaliteta ili samo oznaka za visokorizične bolesnike (teška kalcifikacija, krući zalisci). U ovoj studiji AR je bila neovisni prediktor mortaliteta u prilagođenoj analizi, ali naravno takve prilagodbe rijetko mogu eliminirati zbunjujuće podatke u cijelosti.

Preživljavanje u studijama PARTNER A i PARTNER B je bilo iznimno dobro. Pojava MU i perivalvularnog propuštanja povezanog sa Sapien valvulom zahtijeva daljnji razvoj ovog uređaja.

Dvije velike studije se provode sa Sapien XT uređajem: PARTNER II studija i istraživanje ARTE. U ovoj drugoj studiji se uspoređuje učinkovitost acetilsalicilatne kiseline u odnosu na kombinaciju acetilsalicilatne kiseline i klopidogreala nakon TAVR kod prevencije velikih ishemijskih događaja.[45]

Nedavno je započela PARTNER II studija.[45] Sastoji se od dvije skupine: kohorte A i kohorte B. Kohorta A će imati 2.000 bolesnika s procjenom rizika STS ≥4. Bit će randomizirani u omjeru 1 : 1 za TAVR s Edwards Sapien XT valvulom ili kirurškom AVR. Postojat će dodatno grupiranje na temelju prisutnosti koronarne bolesti srca (CAD). Bolesnici s CAD će biti randomizirani u omjeru 1 : 1 za TAVR i perkutanu koronarnu intervenciju, odnosno na kirurški AVR i CABG. Kod svih bolesnika bit će učinjena detaljna procjena prije i nakon postupka. Prikupit će se podaci i za podstudiju o ukupnom psihofizičkom stanju ispitanika. Kohorta B će imati 500 neoperabilnih bolesnika koji će biti randomizirani u omjeru 1 : 1 za TAVR s Edwards Sapien THV i Edwards Sapien XT uređajima. Usporediti će se sigurnost i učinkovitost ova dva uređaja. Očekuje se da će studija završiti 2018. god.

Edwards Lifesciences (SAD) je razvio dvije nove valvule: Centera i Sapien III valvula. Oba ova uređaja su u fazi ispitivanja prve primjene na ljudima.

Osim Sapien uređaja, jedini drugi uređaj odobren od FDA je CoreValve (Medtronic Inc, Minneapolis, Minnesota, SAD). Sadrži listiće svinjskog perikarda postavljenih na samoekspandirajući nitinolski okvir. Ne dopušta antegradnu im-

major bleeding (19.5% vs 9.3% at 30 days; 25.7% vs 14.7% at 1 year) and new AF (16.0% vs 8.6% at 30 days; 17.1% vs 12.1% at 1 year).

Both surgical AVR and TAVR resulted in a decrease in aortic valve gradients and an increase in effective orifice area (EOA) ($p<0.0001$) which remained stable over 2 years. TAVR was associated with higher indexed EOA, lower prosthesis-patient mismatch, and more aortic regurgitation (AR).[48]

Though right ventricular function is reduced following surgical AVR, there is no such effect with TAVR.[49,50]

A recent study has shown that there is transient systolic and diastolic dysfunction within the first 24 h of a successful TAVR.[51] This is associated with an increase in serum markers of myocardial injury and dysfunction suggesting that the postprocedural dysfunction is due to myocardial stunning and periprocedural injury to the myocardium.

Post-procedure paravalvular AR is more common after TAVR than after surgery.[52,53] We have learned from the PARTNER trials data, confirmed by subsequent studies, that there is an association of post-TAVR paravalvular leak and increased mortality. Based on the German TAVR registry, the occurrence of significant angiographically assessed AR immediately after TAVR was 17.2%. This population consisted of 84% Medtronic CoreValve systems and 16% Edwards Sapien valves. The risk for in-hospital mortality was increased around 2.5-fold in patients with significant AR.[52] However, whether AR is a cause for mortality or just a marker for higher risk patients (severe calcification, tighter valves) is unclear. In this study, AR was an independent predictor of mortality in an adjusted analysis, but of course such adjustments are rarely able to eliminate confounding entirely.

The survival in both the PARTNER A and PARTNER B trials was remarkably good. But stroke and perivalvular leakage associated with the Sapien valve required further evolution of the device.

Two large studies are being conducted with the Sapien XT device: the PARTNER II study and the ARTE (Aspirin Versus Aspirin and Clopidogrel Following Transcatheter Aortic Valve Implantation) trial. The later study is comparing the efficacy of aspirin versus a combination of aspirin and clopidogrel following TAVR in preventing major ischaemic events.[45]

The PARTNER II study has recently started.45 It consists of two arms: cohorts A and B. Cohort A will have 2,000 patients with an STS risk score of ≥4. They will be randomised on a 1 : 1 basis to TAVR with the Edwards Sapien XT valve or to surgical AVR. There will be substratification based on coronary artery disease (CAD). Patients with CAD will be randomised on a 1 : 1 basis to TAVR plus percutaneous coronary intervention and to surgical AVR plus CABG. A detailed pre- and post-procedural logical assessment will be done on all patients. Data for a frailty substudy will also be collected. Cohort B will have 500 inoperable patients who will be randomised on a 1 : 1 basis to TAVR with the Edwards Sapien THV and Edwards Sapien XT devices. The safety and efficacy of the two devices will be compared. The study is expected to finish in 2018.

Edwards Lifesciences (USA) has developed two additional valves: the Centera and the Sapien III valves. Both these devices have recently entered first-in-man studies.

Other than the Sapien device, the only other FDA approved device is the CoreValve (Medtronic Inc, Minneapolis, Min-

plantaciju za razliku od Sapien valvule koja se može izgraditi i antegradno i retrogradno.[54] No, prednost je da koristi uži promjer sustava uvođenja od 18 French.

U Medtronic CoreValve multicentričnom proširenom evaluacijskom registru, početni uspjeh postupka je bio visok (97%), a proceduralni mortalitet je bio nizak (1,5%).[55] Smrtnost nakon 30 dana od svih uzroka (uključujući i proceduralni) je bio nizak (8%). Ova dobrobit je postojana do 1 godine.[56] Ussia *i sur.* su izvijestili o postojanim kliničkim i funkcionalnim kardiovaskularnim koristima tijekom razdoblja iznad 3 godine. Nedavno predstavljanje rezultata ADVANCE CoreValve registra je pokazalo učestalost mortaliteta od svih uzroka od 1,8% i kardijalnog mortaliteta od 8,4% u 6 mjeseci. Učestalost MU bila je niska (2,9% u 30 dana), a ugradnje elektrostimulatora srca bila je 26,3%.[45]

Ova poprilično visoka stopa ugradnje elektrostimulatora srca se često smatra ograničenjem za CoreValve sustav, kada ga se uspoređuje sa Edwards Sapien sustavom i nakon kirurškog AVR. Nakon kirurškog AVR, nedavna velika kohortna studija kod 780 bolesnika je ukazala na potrebu za ugradnjom elektrostimulatora srca nakon postupka od 3,2%.[57] Međutim, potreba se za elektrostimulatorom srca za samoekspandirajući CoreValve sustav smanjila tijekom vremena s tehničkim usavršavanjima i iskustvom operatora. Valvule se sada ugrađuju na višem položaju što je značajno smanjilo smetnje provođenja.

Oslikavanja magnetskom rezonancijom su ukazala na višestruke male moždane infarkte (u 77% slučajeva) nakon TAVR. Mnoge lezije su bile asimptomatske. Klinički MU je bio povezan s većim brojem i volumenom infarkta.[58] Studija SIMPLIFy TAVI istraživala je da li izbjegavanje balonske valvuloplastike za predilataciju nativne aortne valvule smanjuje rizik od MU tijekom TAVI.

Očekuje se da se u prospektivnom registru CoreValve Advance II definiraju načini za smanjenje potrebe za ugradnjom trajnog elektrostimulatora srca.

TAVR je isto tako uspješno ispitan u nekoliko indikacija, koje nisu službeno odobrene, kod bolesnika s bikuspidnim valvulama, teškom MR, smanjenom ejekcijskom frakcijom lijeve klijetke i u bolesnika s aortnom stenozom niskog gradijenta i malog outputa.[59]

I neke nove valvule su trenutno u fazi razvoja. Tu spadaju Sadra Lotus valvula (Medtronic Inc, Minneapolis, Minnesota, SAD), Direct Flow Medical (DFM) valvula (Direct Flow Medical Inc, Santa Rosa, California, SAD), Symetis Acurate valvula (Symetis SA, Ecublens, Switzerland), JenaValve (JenaValve, Munich, Germany) i Engager valvula.

Uređaji za prevenciju embolije

Nepovoljni cerebrovaskularni događaji se ubrajaju u komplikacije TAVI. Oslikavanjem magnetskom rezonancom otkrilo je subkliničke postproceduralne embolijske lezije nakon postupka TAVR u više od 90% bolesnika.[60] Kako bi se spriječio ovaj problem razvijaju se posebni uređaji za prevenciju embolije. Sustav Claret CE Pro (Claret Medical, Inc, Santa Rosa, California, SAD) se sastoji od dva filtera za hvatanje ostataka koji se kreću u brahiocefaličkoj i lijevoj zajedničkoj karotidnoj arteriji. *Naber i sur.*[61] su opisali korištenje ovog novog uređaja kada je bio prvi put testiran na čovjeku i to kod 40 bolesnika koji su se bili podvrgli TAVI i dokazano je smanjenje proceduralnog broja cerebralnih embolijskih događaja.

nesota, USA). It has porcine pericardial leafiets mounted on a self-expanding nitinol frame. It does not allow antegrade implantation, unlike the Sapien valve which can be implanted both antegrade as well as retrograde.[54] However, the advantage is that it uses a lower profile delivery system of 18 French.

In the Medtronic CoreValve multicentre expanded evaluation registry, the initial procedural success was high (97%) and the procedural mortality was low (1.5%).[55] The 30-day all cause mortality (including procedural) was also low (8%). These benefits were sustained over time up to 1 year.[56] Ussia *et al* reported sustained clinical and functional cardiovascular benefits over 3 years too. A recent presentation of the results of the ADVANCE CoreValve registry revealed an all cause mortality rate of 12.8% and a cardiac mortality rate of 8.4% at 6 months. Stroke rates were low (2.9% at 30 days) while the pacemaker implantation rate was 26.3%.[45]

This rather high rate of pacemaker implantation is often regarded as a limitation for the CoreValve system, when comparing it with the rates for the Edwards Sapien system and with the rate after surgical AVR. After surgical AVR, a recent large cohort study in 780 patients showed a need for a pacemaker implantation post-procedure of 3.2%.[57] However, the need for pacemaker for the self-expandable CoreValve system has decreased over time with technical iterations and operator's experience. The valves are now implanted in a higher position, which has significantly reduced electrical disturbances.

MRI tests have shown multiple small cerebral infarcts (in 77% cases) following TAVR. Most of the lesions were silent. Clinical stroke was associated with higher infarct number and volume.[58] The SIMPLIFy TAVI study (Transcatheter Aortic Valve Implantation Without Predilation) is investigating whether the avoidance of balloon valvuloplasty for predilation of the native aortic valve reduces the stroke risk during TAVI.

The CoreValve Advance II prospective registry is expected to define ways to reduce the need for permanent pacemaker implantation.

TAVR has also been tried successfully in several 'off label' indications such as in patients with bicuspid valves, severe MR, reduced left ventricular ejection fraction, and low gradient, low output AS.[59]

Other valves are currently under evolution. These include the Sadra Lotus valve (Medtronic Inc, Minneapolis, Minnesota, USA), Direct Flow Medical (DFM) valve (Direct Flow Medical Inc, Santa Rosa, California, USA), Symetis Acurate valve (Symetis SA, Ecublens, Switzerland), JenaValve (JenaValve, Munich, Germany), and the Engager valve.

Embolic protection devices

Cerebrovascular adverse events have been reported as complications of TAVI. Also, MRI studies have detected subclinical postprocedural embolic lesions following TAVR in over 90% of patients.[60] To address this issue, specific embolic protection devices are being developed. The Claret CE Pro system (Claret Medical, Inc, Santa Rosa, California, USA) has two filters to capture any debris that moves in the brachiocephalic and left common carotid artery. Naber *et al*[61] described the first-in-man use of this novel device in 40 patients undergoing TAVI with evidence of reduction of procedural cerebral embolic burden.

Uređaj TriGuard Cerebral Protection Device (Keystone Heart, Israel, formerly SMT R&D) djeluje kao odbijač ostataka umjesto sakupljač ostataka. Sličan uređaj je Embrella embolijski odbijač (Edwards Lifesciences, Irvine, California, SAD). I Embrella kao i TriGuard imaju zaštitni štit koji odbija emboliju od cerebralnih arterija.

U SMT FIM (prvo testiranje na čovjeku) studiji izvedivosti je opisana upotreba SHEF uređaja kod prvih 15 bolesnika.62 Od studije DEFLECT I (SMT Embolic Deflection CE Mark), koja je u tijeku, očekuju se dodatni dokazi učinkovitosti ovog uređaja. Prvi rezultati su predstavljeni na EuroPCR u svibnju 2013. u Parizu i pokazuju obećavajuće rezultate. Maksimalna ukupna količina oštećenja DEFLECT I je bila 95% manja nego maksimalna ukupna količina oštećenja u prijašnjim studijama (3,94 naspram 70,3 cm^3).

Iskustvo primjene Embrella uređaja kod ljudi dolazi iz male studije s četiri bolesnika s teškom AS koji su se podvrgli balonskoj aortnoj valvuloplastici ili TAVI.[63] Nije bilo proceduralnih komplikacija. Proceduralna sigurnost, tehnička izvedivost i očekivana učinkovitost Embrella uređaja su bili proučeni u ProTAVI-C pilot studiji u devet centara uključivši 54 bolesnika. Korištenje Embrella odbijača tijekom TAVI je bilo izvedivo i sigurno uz minimalne proceduralne komplikacije. Nije bilo MU tijekom postupka niti oštećenja neurokognitivne funkcije. Iako je bilo cerebralne mikroembolizacije kod svih bolesnika, bilo je značajno smanjenje veličine oštećenja mozga. Druga faza randomizirane studije je provođena u svrhu ispitivanja smanjenja količine novonastalih cerebralnih lezija.

Intervencije na aortnom zalistku — Ključne točke:

• Postoje čvrdti dokazi koji pokazuju pokazuje da je TAVR učinkovit u odnosu na farmakološko liječenje.

• TAVR je neinferioran kirurškom postupku AVR kod visokorizičnih bolesnika, ima neke prednosti, ali je povezan s nešto višim rizikom od MU.

• Studije u tijeku i buduće studije će vjerojatno dokazati neinferiornost TAVR u odnosu na AVR kod srednje rizičnih bolesnika i tako će se dodatno povećavati primjena TAVR.

Renalna denervacija

Približno 5-10% svih hipertenzivnih bolesnika su rezistentni na medikamentozno liječenje, a to se definira kao vrijednost arterijskog tlaka >140/90 mmHg ili >130-139/80-85 mmHg kod dijabetičara ili >130/80 mmHg kod bolesnika s kroničnom bubrežnom bolešću (CKD) uz uzimanje ≥3 antihipertenzivna lijeka različitih vrsta, uključujući i diuretik, u maksimalnoj ili najvišoj toleriranoj dozi. Međutim, rezistentnost je vjerojatno nerijetko uzrokovana nesuradljivošću. S druge strane, nepodnošenje lijekova ili nuspojave nisu rijetke i mogu biti izazov u medikamentoznom zbrinjavanju arterijskog tlaka. Razvoj kateterske radiofrekventne ablacije renalnih simpatičkih živčanih vlakana je vrlo obećavajući novi pristup.

Godine 2009. je objavljena europsko-australska studija dokaza načela, nerandomizirana studija Simplicity HTN-1; obavljena je na 50 bolesnika sa rezistentnom hipertenzijom (tj. sistoličkim arterijskim tlakom ≥160 mmHg na tri ili više antihipertenzivna lijeka, uključujući diuretik).[64] Petoro bolesnika koji anatomski nisu bili podobni za postupak denervacije su bili kontrolna skupina. Nakon radiofrekvencijskog ablacijskog kateterskog postupka (Symplicity, Ardian Inc, Palo Alto, California, SAD), arterijski tlak kod ovih 45 bolesnika je značajno pao tijekom 12 mjesečnog razdoblja (**Slika 3**).

The TriGuard Cerebral Protection Device (Keystone Heart, Israel, formerly SMT R&D) works as a debris defiector instead of a debris collector. A similar device is the Embrella Embolic Defiector (Edwards Lifesciences, Irvine, California, USA). Both Embrella and TriGuard have a protective shield that defiects embolisms away from the cerebral arteries.

The SMT FIM (first in man) feasibility study described the use of the SHEF device in the first 15 patients.[62] The ongoing DEFLECT I (SMT Embolic Deflection CE Mark) study is expected to provide further evidence of the effectiveness of the device. First results have been presented at EuroPCR in May 2013 in Paris and show promising results. The maximum total lesion volume in DEFLECT I was 95% smaller than the maximum total lesion volume in reported studies (3.94 vs 70.3 cm^3).

The human experience with Embrella comes from a small study of four patients with severe AS who underwent aortic balloon valvuloplasty or TAVI.[63] There were no procedural complications. The procedural safety, technical feasibility, and exploratory efficacy of the Embrella device was studied in the ProTAVI-C pilot study at nine centres involving 54 patients. Use of the Embrella defiector system during TAVI was feasible and safe with minimal procedural complications. There were no procedural strokes or impairment of neurocognitive function. Though there was cerebral microembolisation in all patients, there was a potential decrease in cerebral lesion volume. A phase 2 randomised study is being conducted to measure the reduction of new cerebral lesion volume.

Aortic valve interventions — Key points:

• There is strong evidence demonstrating that TAVR is effective compared to medical therapy.

• TAVR is non-inferior to surgical AVR in high risk patients, it has several advantages, but has been associated with a slightly higher stroke risk.

• Ongoing and planned trials looking at the comparative effect of TAVR and AVR in intermediate risk patients are likely to show non-inferiority and may further increase the use of TAVR.

Renal denervation

Approximately 5-10% of all hypertensive patients are resistant to medical treatment, defined as blood pressures >140/90 mmHg or >130-139/80-85 mmHg in diabetic patients or >130/80 mmHg in patients with chronic kidney disease (CKD) in the presence of ≥3 antihypertensives of different classes, including a diuretic, at maximal or the highest tolerated dose. However, 'resistance' is probably not rarely caused by malcompliance. On the other hand, drug intolerance or side effects are not rare and can be a challenge in medical blood pressure management. The development of catheter based radiofrequency ablation of the renal sympathetic nervous fibres is a highly promising new approach.

In 2009, a European-Australian proof-of-principle study, the non-randomised Simplicity HTN-1, was published; it was per- formed on 50 patients with resistant hypertension (ie, systolic blood pressure fi160mmHg on three or more antihypertensive medications, including a diuretic).[64] Five of the patients who were not anatomically eligible for the denervation procedure were used as controls. After this radiofrequency ablation catheter procedure (Symplicity, Ardian Inc, Palo Alto, California, USA), the blood pressure in these 45 patients dropped significantly over a period of 12 months (**Figure 3**).

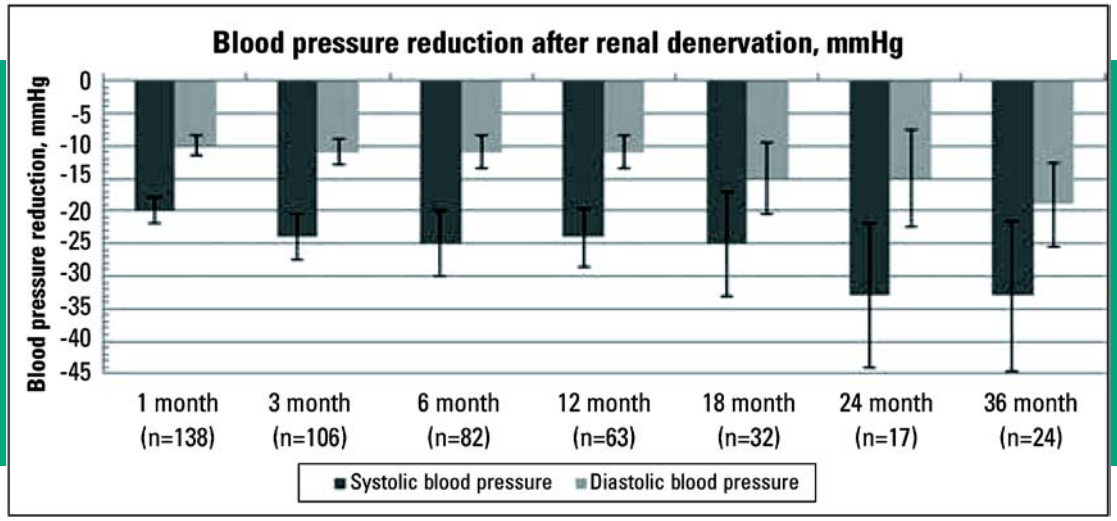

Figure 3. *Blood pressure reduction in systolic and diastolic blood pressure up to 1, 3, 6, 12, 18, 24, and 36 months after renal denervation.*

Proširena kohorta od 153 bolesnika s rezistentnom hipertenzijom je analizirana u studiji Simplicity HTN-1.[65] Bolesnici su bili liječeni kateterskom renalnom simpatetičkom denervacijom u 19 centara u Australiji, Europi i SAD. Studija je pokazala značajno i održano smanjenje arterijskog tlaka tijekom razdoblja praćenja od ≥2 godine, bez ikakvih značajnih nuspojava. Simplicity HTN-1 je bila studija izvedivosti i nije imala kontrolnu grupu. Naknadno je Simplicity HTN-2 ispitivanje randomiziralo 106 bolesnika za renalnu denervaciju ili kontrolu.[66] U šestomjesečnom razdoblju arterijski tlak u skupini na renalnoj denervaciji je bio značajno niži. Nakon šestomjesečnog razdoblja, učinjeno je ukriženje i dopuštena je renalna denervacija kod kontrolnih bolesnika.[67] U početnoj renalnoj denervacijskoj skupini, značajno smanjenje srednjeg arterijskog tlaka u 6 mjeseci (32 mmHg) je bilo održano u razdoblju od 12 mjeseci (28 mmHg). U razdoblju od 6 mjeseci, kontrolna grupa je pokazala povećanje tlaka od 182,8±16,3 do 190,0±19,6mmHg. Oni koji su među ovom kontrolnom grupom bili podvrgnuti renalnoj denervaciji kao ukriženju imali su značajan pad arterijskog tlaka u 6 mjesečnom razdoblju nakon postupka (24 mmHg; p<0.001 za razliku od razdoblja prije ovog postupka). Ovim se potkrijepila sigurnost i učinkovitost renalne denervacije kontroliranom radiofrekvencijskom ablacijom.

Studija Simplicity HTN-2 nije pratila 24 h vrijednosti arterijskog tlaka. Nije bila dizajnirana kao slijepa studija. Te metodološke zahtjeve se postavilo u studiji Simplicity HTN-3.[67] To je multicentrična, pojedinačna, jednostruko slijepa, randomizirana, kontrolirana studija gdje su bolesnici randomizirani u skupinu s provedenom bilateralnom renalnom denervacijom s Simplicity kateterom ili u skupinu s provedenim placebo postupkom. Jedna od važnih sekundarnih ishodišnih rezultata ove studije je promjena u 24 h arterijskom tlaku.

Uređaj za renalnu denervaciju Simplicity je također ispitan na drugim skupinama bolesnika kao što je pilot studija bolesnika s rezistentnom hipertenzijom i umjerenom do srednje teškom (faza 3 ili 4) kroničnom renalnom insuficijencijom.[68] Utvrđeno je da je primjena sigurna i učinkovita. Studija Simplicity HF trenutno je uključila 40 bolesnika za pilot studiju radi ocjene učinaka renalne denervacije kod bolesnika s srčanim zatajivanjem. U kliničkoj praksi se očekuje da globalni Simplicity registar uključi 5.000 bolesnika na 200 lokacija diljem svijeta. U registar je do 25. svibnja 2013. god.

An expanded cohort of 153 patients with resistant hypertension was studied in the Simplicity HTN-1 study.[65] The patients were treated with catheter based renal sympathetic denervation at 19 centres in Australia, Europe, and the USA. They showed a substantial and sustained reduction of blood pressure over a follow up of ≥2 years without any significant adverse effects. Simplicity HTN-1 was a feasibility stud and had no control group. The subsequent Simplicity HTN-2 trial randomised 106 patients to renal denervation or control.[66] At 6 months, the blood pressure in the treatment group was significantly lower. After the 6-month end point, a crossover was done and renal denervation in control patients was allowed.[67] In the initial renal denervation group, the significant reduction in mean blood pressure at 6 months (32 mmHg) was sustained at 12 months (28 mmHg). At 6 months, the control group had shown an increase in blood pressure from 182.8±16.3 to 190.0±19.6mmHg. Those among this control group who underwent renal denervation as crossover had a significant fall in their blood pressure at 6 months after the procedure (fi24mmHg; p<0.001 for difference from before the procedure). This substantiated the safety and efficacy of renal denervation via controlled radiofrequency ablation.

The Simplicity HTN-2 study did not report on the 24 h blood pressure monitoring. It was not a blinded study design. These methodological issues are being addressed in the Simplicity HTN-3 study.[67] It is a multicentre, single blind, randomised controlled trial where patients are being randomised to bilateral renal denervation with the Simplicity catheter or to a sham procedure. One of the important secondary end points of the study is the change in 24 h blood pressure.

The Simplicity renal denervation device has also been tried in other patient groups, such as in a pilot study of patients with resistant hypertension and moderate to severe (stage 3 or 4) CKD.[68] It was found to be safe and effective. The Simplicity HF study is currently enrolling 40 patients for a pilot study to evaluate the effects of renal denervation in heart failure patients. In the real world setting, the Global Simplicity Registry is expected to enrol 5,000 patients in 200 sites worldwide. The registry had enrolled 617 patients by 25 May 2013. Based on preliminary data presented at the EuroPCR 2013, there have been significant drops in in-

uključeno 617 bolesnika. Na temelju preliminarnih podataka predstavljenih na EuroPCR 2013, postignut je značajan pad arterijskog tlaka mjerenog u liječničkoj ordinaciji i 24 h arterijskog tlaka. Ova smanjenja su, međutim manja od onih koja se vide u kliničkim ispitivanjima.

Na EuroPCR 2013. predstavljeni su privremeni podaci prva 41 bolesnika liječena u studiji REDUCE-HTN[69] sustavom Vessix renalne denervacije. U šestomjesečnom razdoblju došlo je do značajnog smanjenja arterijskog tlaka (27,6 mmHg; p<0.0001). Kod tih bolesnika za koje su bili dostupni 12-mjesečni podaci postojalo je značajno smanjenje sistoličkog arterijskog tlaka (28,4 mmHg). Nije bilo nepovoljnih događaja povezanih s uređajem niti komplikacija tijekom postupka te je vrijeme postupka bilo kratko.

EnlighHTN multielektrodni kateter za renalnu denervaciju (St. Jude Medical) je ispitan na 46 bolesnika koji su bili praćeni u razdoblju od 1 godine.[70] Većina bolesnika (80%) je odgovorila na terapiju (imali su najmanje 10 mmHg smanjenja srednjeg arterijskog tlaka). Srednje smanjenje arterijskog tlaka u 12 mjesečnom razdoblju je bilo 27 mmHg. Multielektrodni uređaj smanjuje vrijeme renalne denervacije te je manje bolno za bolesnike. Ostali uređaji sa multimodalnim pristupom uključuju Covidien One-Shot uređaj i modifikaciju Simplicity uređaja pod nazivom Spyral uređaj.

Trenutno se renalna denervacija smatra dodatnom terapijom uz medikamentozno liječenje, a ne zamjenom, budući da se prosječan broj bolesnika koji su uzimali antihipertenzivne lijekove nije smanjio u ispitivanjima unatoč smanjenju srednjeg arterijskog tlaka nakon renalne denervacije.[70]

Iako postoji puno uzbuđenja oko ove nove metode liječenja rezistentne hipertenzije, postoji zabrinutost o difuznom suženje renalnih arterija i oštećenju tkiva na mjestu ablacije, uz formiranje edema i tromba koji se mogu pojaviti nakon ablacije renalnog živca.[71] Stoga je možda potrebna dvojna antiagregacijska terapija tijekom postupka. Iako je renalna denervacija pokušana kod bolesnika s CKD,[68] bolesnici s visokim stupnjem renalne insuficijencije bi se trebali samo liječiti i sistematski pratiti u kliničkim ispitivanjima. Također se ne treba postupak provoditi kod anatomski nepodobnih renalnih arterija (promjera <4 mm, dužina <20 mm; kod fibromuskularne displazije; značajne stenoze renalnih arterija) ili u slučajevima sekundarnih i izlječivih uzroka hipertenzije.[72] Također moramo biti svjesni da nema podataka o utjecaju renalne denervacije na kliničke ishode u ovoj fazi. Njezina primjena bi se stoga trebala ograničiti na bolesnike s teškom, rezistentnom hipertenzijom i trebala bi se smatrati dodatnom, a ne alternativnom terapijom antihipertenzivnim lijekovima.

Renalna denervacija — Ključne točke:

• Renalna denervacija predstavlja obećavajući pristup liječenju rezistentne hipertenzije, njezin učinak na smanjenje arterijskog tlaka je impresivan, ali buduće studije trebaju dokazati da će ista dovesti do poboljšanih kliničkih ishoda.

• Slično kao i TAVR, moguće je da će se indikacija za ovaj postupak dalje proširiti na nerezistentnu hipertenziju i ostala područja, kao što su zatajivanje srca, kontrola srčane frekvencije kod FA, itd.

Zaključak

Dok postoji jasan značajan tehnološki napredak u perkutanim koronarnim intervencijama,[73] revolucionarne su sve veće mogućnosti liječenja nekoronarne srčane bolesti kateterskim tehnikama. Neki od ovih postupaka su razvijani za bo-

office blood pressure and 24 h blood pressure. These reductions are, however, smaller than those seen in clinical trials.

At the EuroPCR 2013, interim data from the first 41 patients treated with the alternative Vessix renal denervation system in its REDUCE-HTN study were presented.[69] At 6 months, there was a significant reduction in blood pressure (27.6 mmHg; p<0.0001). In those patients for whom 12-month data were available, there was a sustained reduction in systolic blood pressure (28.4 mm Hg). There were no device related adverse events or procedural complications and the procedure time was short.

The EnlighHTN multielectrode renal denervation catheter (St Jude Medical) has been tried in 46 patients who were then followed up for 1 year.[70] Most patients (80%) responded to therapy (had at least 10 mmHg reduction in mean blood pressure). The mean reduction in blood pressure at 12 months was 27 mmHg. The multielectrode device reduces the renal denervation time and is also less painful to patients. Other devices with a multimode approach include the Covidien One-Shot device and a modification of the Simplicity device called the Spyral device.

Currently, renal denervation is considered an adjunctive therapy to medical treatment, not a replacement, since the average number of patients taking antihypertensive medications has not declined in the trials in spite of the reduction in mean blood pressure following renal denervation.70

Although there is a lot of excitement about this new modality of treatment for resistant hypertension, there are concerns about the diffuse renal artery constriction and tissue damage at the ablation site, with oedema and thrombus formation that may occur following renal nerve ablation.[71] Dual antiplatelet therapy may therefore be needed during the procedure. Even though renal denervation has been tried in patients with CKD,[68] patients with high grades of renal insufficiency should only be treated and systematically followed in clinical trials. It should also not be tried in anatomically unsuitable renal arteries (diameter <4 mm; length <20 mm; fibromuscular dysplasia; significant renal artery stenosis) or in cases of secondary and treatable causes of hypertension.[72] We also have to be aware that there are no data on the impact of renal denervation on clinical outcomes at this stage. Its use should therefore be restricted to patients with severe, resistant hypertension and it should be regarded as an adjunctive and not an alternative therapy to antihypertensive drugs.

Renal denervation — Key points:

• Renal denervation is a promising approach to treat resistant hypertension, its effect on blood pressure reduction is impressive, but future studies need to prove that this translates into improved clinical outcomes.

• Similar to TAVR, it is likely that the indication for this procedure will further expand to non-resistant hypertension and to other areas such as heart failure, rate control for AF, etc.

Conclusion

While there is clearly significant technological progress in percutaneous coronary interventions,[73] the expanding options to treat non-coronary cardiac disease with catheter based techniques are revolutionary. Several of these procedures have been developed for very high surgical risk or 'no option' patients, such as TAVR, but are increasingly used in high risk or even intermediate risk patients as a less inva-

lesnike s visokim operativnin rizikom ili bolesnike bez druge mogućnosti liječenja kao što je TAVR, ali se sve više primjenjuju i kod visokorizičnih ili čak srednje rizičnih bolesnika kao manje invazivna alternativa kirurškom zahvatu. Brz tehnološki napredak, sve veće razumijevanje i usavršavanje operatora će doprinijeti proširenju indikacija za ove postupke i kod bolesnika s nižim rizikom ta za primjene za druge indikacije. Renalna denervacija primjerice može pokazati dobrobit kod bolesnika sa srčanim zatajivanjem ili za kontrolu srčane frekvencije kod FA.

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sive alternative to surgery. The fast technological progress, increasing understanding, and improvements in the operators' experience will further expand the indications for these procedures to lower risk patients and for applications for other indications. Renal denervation, as an example, may show benefit in patients with heart failure or for rate control in AF.

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