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Prva iskustva u primeni rivaroksabana kod bolesnika sa plućnom tromboembolijom koji su primali trombolitičku terapiju

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Sažetak

Uvod. Novi – direktni antikoagulantni lekovi su ušli u najnovije preporuke za lečenje plućne tromboembolije (PTE). Međutim, nepoznato je da li se i na koji način ovi lekovi mogu koristiti u lečenju bolesnika sa PTE nakon primene trombolitičke terapije jer su ovi bolesnici isključivani iz svih randomizovanih studija.

Pacijenti. Analizirali smo ishod lečenja kod 101 bolesnika sa PTE koji su lečeni u Klinici za urgentnu internu medicinu VMA od 2010. do 2014. godine. Kod 53 bolesnika su nakon inicijalne terapije heparinima uvedeni vitamin K antagonisti, 9 bolesnika je bilo na heparinima, 37 bolesnika je primalo rivaroksaban i kod 3 bolesnika je dat dabigatran kao antikoagulans.

Rezultati. Intrahospitalna smrt je zabeležena kod 11,1 % (1/8) bolesnika na rivaroksabanu bez trombolize, kod 0 % (0/28) bolesnika koji su primali rivaroksaban i trombolizu, kod 4,8 % (1/20) bolesnika na vitamin K antagonistima bez trombolize, kod 0 % (0/32) bolesnika na vitamin K antagonistima i trombolizi, kod 75 % (6/2) bolesnika koji su dobijali samo heparin i 0 % kod bolesnika na dabigatranu (0/3). Šestomesečna smrt je zabeležena kod 22,2 % (2/7) bolesnika samo na rivaroxabanu, kod 3,6 % (1/26) bolesnika sa trombolizom i rivaroksabanom, kod 19 % (4/17) bolesnika sa vitamin K antagonistima bez trombolize, kod 3,1 % (1/31) bolesnika sa vitamin K antagonistima nakon trombolize, kod 87,5 % (7/1) bolesnika samo na heparinu i kod nijednog bolesnika samo na dabigatranu (0/3). Značajna krvarenja su zabeležena iskljuvo intrahospitalno i to kod 25 % bolesnika na rivaroksabanu nakon trombolize i kod 18,8 % kod bolesnika na vitamin K anagonistima nakon trombolize (p=ns). Nije bilo fatalnih krvarenja.

Zaključak. Rivaroksaban je verovatno podjednako bezbedan i efikasan u poređenju sa klasičnim lečenjem (heparini i prevođenje na vitamin K antagoniste) kod pacijenata sa PTE nakon primene trombolitičke terapije.

Ključne reči plućna embolija, rivoraksaban, trombolitička terapija

Uvod

Tokom poslednjih nekoliko godina novi direktni oralni antikoagulansi su zahvaljujući rezultatima iz velikih randomiziranih studija ušli u široku upotrebu kod prevencije tromboembolizma nakon zamene kuka i kolena endoprotezama, u prevenciji moždanog udara kod bolesnika sa atrijalnom fibrilacijom i u lečenje venskog tromboembolizma, što uključuje i bolesnike sa dubokom venskom trombozom i plućnom tromboembolijom. Ovi lekovi su bili najmanje podjednako efikasni kao klasična kombinacija niskomolekularnog heparina i vitamin K antagonista, a ispoljili su značajno veću bezbednost, tj. manje hemoragijskih komplikacija[1–7]. Prednost ovih lekova je u tome što određena peroralno data doza ima predvidljiv antikoagulantni učinak i nije potrebno merenje antikoagulantne aktivnosti sem u posebnim slučajevima (krvarenje ili neophodnost hitne hirurške intervencije) i što hrana i lekovi mnogo manje nego kad su u pitanju vitamin K antagonisti utiču na njihov antikoagulantni efekat[8].

Kada su u pitanju duboke venske tromboze i plućne tromboembolije, zahvaljujući velikim randomiziranim studijama i dabigatran (RECOVER I i II)[2,3], i rivaroxaban (EINSTEIN-DVT i EINSTEIN-PE)[4,5], i apixaban (AMPLIFY)[6], i edoksaban (HOKUSAI-VTA)[7] ušli su u preporuke za lečenje bolesnika sa DVT/PTE ukoliko pacijenti nemaju tešku bubrežnu insuficijenciju (klirens kreatinina za rivaroxaban i apiksaban ispod 15 ml/min., a za dabigatran 30 ml/min.)[1].

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Međutim, sve pomenute studije su isključivale bolesnike koji su primili trombolitičku terapiju tako da nemamo podatke za tu grupu bolesnika. Poseban problem kod ove grupe bolesnika je kako i kada uključiti nove oralne antikoagulanse. Cilj ovog rada je da se prikažu iskustva sa primenom rivaroksabana u lečenju akutne PTE, a naročito da se pokažu rezultati primene kod bolesnika koji su dobili PTE zbog hemodinamske nestabilnosti i/ili izražene disfunkcije desne komore.

Metodologija

U periodu od 2010. godine do novembra 2014. godine na Klinici za urgentnu internu medicinu lečen je 101 bolesnik sa skenerskom angiografijom dokazanom PTE. Prosečne godine bolesnika su bile 60±17, a žene su bile nešto više zastupljene (53, 52,5 %). Osnovne karakteristike bolesnika su prikazane u tabeli 1. Na prijemu bolesnika se na osnovu kliničke slike (arterijski krvni pritisak i srčana frekvenca), nalaza gasova u arterijskoj krvi, ehokardiografskog i nalaza na MDCT plućno angiografiji procenjivao rizik za umiranje od PTE i za eventualno razvijanje posledične sekundarne plućne hipertenzije. Bolesnici koji su bili tahikardični (SF>100 u min.), hipotenzivni (sistolni pritisak<90 mmHg), koji su imali tešku hipoksemiju (pO2<50 mmHg u arterijskoj krvi) sa znacima opterećenja DK (SPDK>40 mmHg i odnos DK/LK u dijastoli na MDCS>1) smatrani su da su pod visokim rizikom i ukoliko nisu imali kontraindikacija nakon obavljene dijagnostike, lečeni su trombolitičkom terapijom. Bolesnici sa hipotenzijom u šoku lečeni su brzim protokolima (alteplaza 0,9 mg/kg za 2 sata, ili tenekteplaza prema kg telesne težine, ili streptokinaza 1500.000 jedinica tokom 2 sata), a bolesnici koji nisu bili u šoku lečeni su prolongiranim protokolima (streptokinaza 100.000 j/sat od 1.500.000 do 3.000.000 jedinica u ukupnoj dozi, ili ultrazvučno-olakšanom kateterskom trombolizom sa alteplazom u dozi od 2 do 3 mg/sat u ukupnoj dozi od 50 do 80 mg). Nakon inicijalne primene trombolitika pacijenti su još 24 sata najmanje, ili do hemodinamske stabilizacije, bili na kontinuiranom heparinu uz preciznu kontrolu aktiviranog parcijalnog tromboplastinskog vremena i monitoring fibrinogena, ostalih hemostaznih parametara i krvne slike. Nakon kontinuirane infuzije heparina prešlo bi se na frakcionisani heparin uz najmanje petodnevno preklapanje za vitamin K antagonistima ili bi se direktno prešlo na primenu rivaroxabana u početnoj dozi od 15 mg na 12 sati uz obroke. Pre otpusta iz bolnice pacijentima bi se obavezno uradio kontrolni ultrazvučni pregled za procenu funkcije desne komore i kontrolna MDCT-PA ili perfuziona scintigrafija pluća. Kliničke i laboratorijske kontrole su se zakazivale na mesec, 3 meseca (kada se obavezno radi i ehokardiografska kontrola) i posle na 6 meseci od otpusta. U slučaju potrebe radili bi se ponovo MDCT-PA i scintigrafija pluća. Značajno krvarenje je praćeno sve vreme po ISTH (International Society of Thrombosis and Haemostasis)[9] kriterijumima (fatalno krvarenje, krvarenje u kritičnim zonama ili organima i pad krvne slike za više od 20 g/L i potreba za transfuzijom krvi). Smrtni ishodi su definisani prema etiologiji na one koji su verovatno posledica PTE i na one koji nisu.

Rezultati

Od ukupno 101 bolesnika sa PTE, 37 je dobilo rivaroksaban tokom hospitalizacije i nastavilo vanbolničko lečenje, dok su vitamin K antagonsti uvedeni nakon inicijalne terapije heparinima kod 53 bolesnika, samo heparine je dobijalo 8 bolesnika (bolesnici koji su umrli pre nego što im se uvela oralna antikoagulantna terapija i bolesnici sa malignim bolestima koji su nastavili da primaju prolongirano frakcionisani heparin kao osnovni antikoagulans) i 3 bolesnika je dobilo dabigatran kao antikoagulantni lek. Osnovne osobine bolesnika, cele grupe i grupe u kojoj je uveden rivaroksaban, a koja je podeljena na grupu koja je dobijala trombolitičku terapiju i na grupu koja nije, prikazane su u tabeli 1.

Glavni ishodi lečenja, smrtnost u bolnici i u periodu praćenja od 6 meseci, kao i verovatni uzroci smrti i učestalost

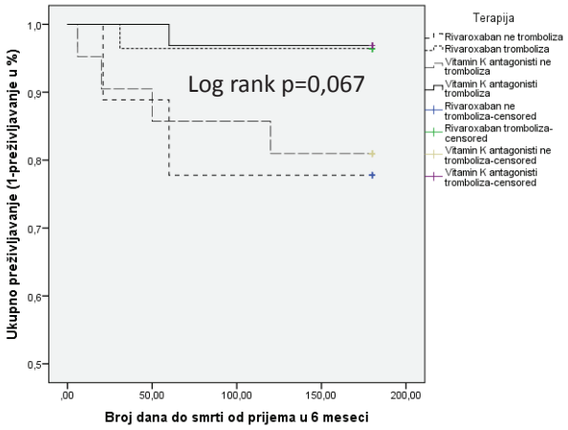
Tabela 1. Osnovne karakteristike bolesnika sa PTE u odnosu na primenu rivaroksabana i rivaroksabana nakon trombolitičke terapije

Osnovne osobine bolesnika	Svi bolesnici N=101	Rivaroxaban Ne-tromboliza N=9	Rivaroxaban Tromboliza N=28
Godine	60±17	59±15	61±15
Pol – žene (%)	53 (52,5)	5 (55,6)	14 (50,0)
Hirurgija pre PTE – n (%)	21 (20,8)	1 (11,1)	9 (32,1)
Aktivno pušenje	24 (23,8)	2 (22,2)	5 (18,5)
Maligna bolest	11 (10,9)	1 (11,1)	1 (3,6)
Simptomatska DVT	56 (55,4)	6 (66,7)	16 (57,1)
PESI skor – n (%)[1]	1 (0-2)	1 (0-3)	1 (0-2)
0	31 (30,7)	5 (55,6)	10 (35,7)
1	25 (24,8)	1 (11,1)	9 (32,1)
2	20 (19,8)	1 (11,1)	4 (14,3)
3 i više	19 (18,8)	2 (22,2)	5 (17,9)
Šokni indeks>1 – n (%)	41 (40,6)	3 (33,3)	10 (35,7)
Hipotenzija <90 mmHg – n (%)	18 (17,8)	0 (0,0)	4 (14,3)
SPDK na prijemu – mmHg±SD	51,3±17,0	34,4±15,6	57,7±17,4
Odnos DK/LK u dijastoli >0,9 MDCT	53 (52,5)	3 (33,3)	18 (64,3)
Trombolitička terapija	64 (63,4)	0 (0,0)	28 (100,0)

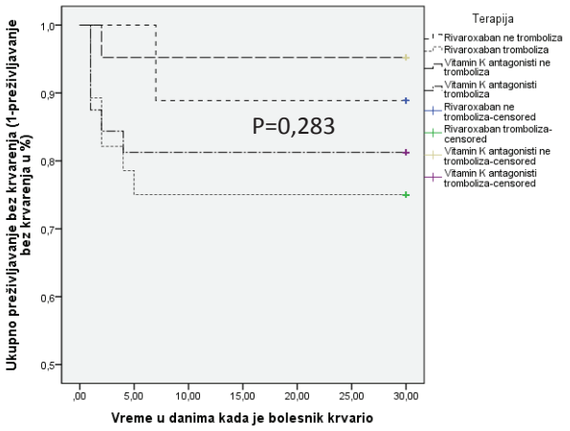
[1]Pojednostavljeni PESI skor se nije mogao izračunati za bolesnike kod kojih nismo imali sve podatke za izračunavanje skora.

Tabele 2. Ishod lečenja PTE u periodu od 6 meseci u odnosu na primenu rivaroksabana i trombolitika

Najvažniji klinički ishodi	Svi bolesnici N=101	Rivaroxaban Ne-tromboliza N=9	Rivaroxaban Tromboliza N=28
Intrahospitalna smrt – n (%)	8 (7,9)	1 (11,1)	0 (0,0)
Smrt unutar 6 meseci – n (%)	15 (14,9)	2 (22,2)	1 (3,6)
PTE uzrok smrti – n (%)	7 (6,9)	0 (0,0)	1 (3,6)
Drugi uzroci – n (%)	8 (7,9)	2 (22,2)	0 (0,0)
Veliko krvarenje – n (%)	15 (14,9)	1 (11,1)	7 (25,0)
Fatalno krvarenje – n (%)	0 (0,0)	0 (0,0)	0 (0,0)



Slika 1. Kaplan-Meierove krive preživljavanja u 6 meseci u zavisnosti od primenjene oralne antikoagulantne terapije (vitamin K antagonisti vs rivaroxaban)



Slika 2. Kaplan-Meierove krive, preživljavanje bez značajnog krvarenja

značajnog krvarenja zbirno je prikazana u tabeli 2 i u grafikonima 1 i 2. Smrtnost unutar 6 meseci je bila 3,6 % (1/27) kod bolesnika koji su primili trombilitičku terapiju i posle toga prevedeni na rivaroksaban, a 3,1 % (1/31) kod bolesnika koji su primili trombolitičku terapiju i prevedeni na vitamin K antagoniste. Značajno krvarenje je dijagnostikovano kod 25 % (7/21) bolesnika sa rivaroksabanom nakon trombolize i kod 18,8 % (6/26) bolesnika koji su nakon trombolize prevedeni na vitamin K antagoniste, p=0,755. Jedan bolesnik (1,6 % od bolesnika koji su primali trombolitičku terapiju) je imao intrakranijalnu hemoragiju (subarahnoidalnu hemoragiju i manju intracerebralnu hemoragiju) nakon trombolize i nakon 2 tablete rivaroksabana, što je iziskivalo potpun prekid antikoagulantne terapije na 21 dan nakon čega je pacijent otpušten sa 10 mg rivaroksabana dnevno. Nisu zabeležena fatalna krvarenja iako je trombolitička terapija primenjena kod 64 bolesnika. Sva značajna krvarenja su uglavnom zabeležena u prvih 5 dana lečenja i zahtevala su najčešće gastroskopiju u slučaju gastrointestinalnih krvarenja koja su bila najčešća, intenzivnu primenu inhibitora protonske pumpe, 2–4 jedinice deplazmatisane krvi i 300–600 ml sveže zamrznute plazme i prekid antikoagulantne terapije od 1 do 3 dana. Kod bolesnika sa subarahnoidalnom hemoragijom smo primenili sveže zamrznutu plazmu 600 ml i 1000 mg traneksamične kiseline uz uvođenje nimodipina, što je stabilizovalo bolesnika bez neurološkog deficita. U periodu od 6 meseci nisu registrovani simptomatski recidivi DVT i PTE osim mogućeg fatalnog recidiva PTE i iznenadne smrti kod bolesnika sa već opisanom intrakranijalnom hemoragijom 7 dana nakon otpusta iz bolnice. Drugi značajniji neželjeni efekti rivaroksabana nisu zabeleženi sem kratkotrajnog prolaznog porasta transaminaza kod jedne bolesnice za 3 puta više od normalnih vrednosti što se moglo pripisati leku s obzirom da nisu nađeni drugi razlozi za ovaj porast.

Diskusija

U našoj studiji smo prikazali rezultate lečenja 37 bolesnika koji su primali rivaroksaban kao osnovni koagulans u lečenju plućne tromboembolije od kojih je 28 bolesnika primilo trombolitičku terapiju. Nije nađena značajna razlika u smrtnosti tokom 6 meseci kod bolesnika koji su lečeni trombolizom i vitamin K antagonistima u odnosu na trombolizu i rivaroksaban. Bolesnici koji su primali trombolitičku terapiju i koji su prevedeni na rivaroksaban su imali nešto češće značajno krvarenje od bolesnika koji su nakon trombolize prevedeni na vitamin K antagoniste, ali ova razlika nije dostigla značajnost. Ono što je bitno nije bilo fatalnih krvarenja ni na rivaroksabanu ni na vitamin K antagonistima, a samo jedan bolesnik je imao nefatalnu intrakranijalnu hemoragiju.
Rezultati naše studije ukazuju da je rivaroksaban verovatno jednako efikasan i bezbedan za primenu i kod bolesnika sa PTE i nakon što su primili trombolitičku terapiju. Većina krvarenja su verovatno vezana upravo za primenu trombolitičke terapije i dogodila su se unutar 3 dana od primene trombolitika, a nisu zabeležena značajnija krvarenja nakon izlaska iz bolesnice. Svi bolesnici su po izlasku iz bolnice bar mesec dana bili na pantoprazolu u jednoj dozi od 20 mg na dan.

Takođe smo mišljenja da je primena trombolitika kod bolesnika sa intermedijarnim rizikom PTE, koja je po najnovijim preporukama klasa III nivo dokaza B[1], neopravdana jer se ne može na osnovu jedne studije u kojoj je primenjen jedan trombolitik, i to za bolus primenu, odrediti taj nivo preporuka. Mišljenja sam da je trebalo primenu ostalih trombolitičkih protokola za sada staviti pod IIb C, naročito imajući u vidu da su bolesnici iz PEITHO studije[10] bili relativno laki – tj. kriterijumi za postavljanje disfunkcije desne komore su suviše laki, a grupa bolesnika je bila relativno stara (66±15 godina), što je u isto vreme smanjivalo šansu za smrtni ishod usled PTE a povećavalo šansu za krvarenje.
U najnovijim preporukama je napravljen veliki napredak sa uvođenjem novih antikoagulantnih lekova, ali nažalost na uštrb primene reperfuzione terapije jer nisu urađene studije koje su kombinovale trombolitičku terapiju i nove antikoagulantne lekove i nedovoljno dobro su definisani bolesnici koji mogu imati korist od reperfuzione terapije pogotovo imajući u vidu i kasne komplikacije PTE, tj. sekundarnu plućnu hipertenziju.

Zaključak

Rivaroksaban se može primeniti kao nastavak antikoagulantne terapije nakon inicijalne primene nefrakcionisanog heparina kod bolesnika sa PTE koji su po prijemu lečeni trombolitičkom terapijom uz pažljivu procenu hemostaznih parametara i faktora koji mogu povećati rizik od krvarenja.

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Abstract

First experiences in the implementation of rivaroxaban in patients with pulmonary thromboembolism who received thrombolytic therapy

Slobodan Obradović, Boris Džudović, Snježana Vukotić, Danijela Vraneš, Miodrag Šipčić, Lidija Torbica, Nenad Ratković, Veljko Milić, Bojana Subotić, Anđelka Ristić

Clinic of Emergency medicine, Military Medical Academy, School of Medicine, University of Defense, Belgrade

Background. *New direct anticoagulant drugs have entered the most recent guidelines for the management of pulmonary thromboembolism (PTE). However, it is still unknown whether and how these drugs could be used in treatment of patients with PTE after they received thrombolytic therapy, because these patients have been excluded from all randomized trials. Patients. We analyzed an outcome of the treatment of 101 patients diagnosed with PTE who were treated in Clinic for emergency end internal medicine in Military Medical Academy in a period 2010–2014. After initial therapy with heparins, 53 patients received vitamin K antagonists, 9 patients remained only on heparins, 37 received rivaroxaban and 3 patients received dabigatran.*
Results. *In-hospital mortality was present in 11.1 % (1/8) of patients on rivaroxaban without thrombolysis, in 0 % (0/28) of patients who were treated with rivaroxaban and thrombolysis, in 4.8 % (1/20) of patients who received vitamin K antagonists without thrombolysis, in 75 % (6/9) of patients treated only with heparins and in 0 % (0/3) of patients treated with dabigatran. Six-month mortality rate was 22.2 % (2/7) of patients treated only with rivaroxaban, 3.6 % (1/26) of patients treated with thrombolysis and rivaroxaban, 19 % (4/17) of patients who received vitamin K antagonists without thrombolysis, 3.1 % (1/31) of patients who received vitamin K antagonists after receiving thrombolysis, 87.5 % (7/9) of patients only on heparins and in none of patients (0/3) treated only with dabigatran. Significant bleeding was noticed only during in-hospital stay and in particular in 25 % of patients treated with rivaroxaban after thrombolysis and in 18 % of patients treated with vitamin K antagonists after thrombolysis (p=ns). There were no fatal bleedings.*
Conclusion. *Rivaroxaban is probably equally safe and effective compared with conventional treatment (heparin and continuation of the vitamin K antagonists) in patients with PTE after administration of thrombolytic therapy.*

Keywords: *pulmonary embolism, rovoroxaban, thrombolytic therapy*

Srce i krvni sudovi 2014; 33(4):231-233

Prikaz pacijenta

Gastrointestinalno krvarenje kod bolesnika sa akutnim infarktom miokarda lečenog primarnom PCI – prikaz slučaja

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Sažetak Sve veća upotreba dvojne antitrombocitne terapije dovela je i do povećanja učestalosti krvarenja iz gastroinestinalnog trakta. Prikazan je slučaj bolesnika starog 54 godine, primljenog u Koronarnu jedinicu iz sale za kateterizaciju srca nakon primarne PCI u okviru akutnog infarkta srca. Na koronarografiji je uočena okludirana desna koronarna arterija u koju je implantiran stent i pacijent je, hemodinamski stabilan, preveden u KJ. Trećeg dana hospitalizacije dolazi do pojave obilne hematemeze, bez ijednog prethodno postojećeg faktora rizika za krvarenje, zbog čega je obustavljena dvojna antitrombocitna terapija, ordinirani inhibitori protonske pumpe i transfuzija krvi. Na ezofagogastroduodenoskopiji uočen je difuzni erozivni gastroduodenitis, sa sluznicom prekrivenom fibrinom. Kako se hematemeza nije više ponavljala, uz gastroenterološko praćenje, u terapiju je postepeno vraćena antitrombocitna terapija, i bolesnik je 16. dana u stabilnom stanju otpušten kući.

Ključne reči gastrointestinalno krvarenje, akutni infarkt miokarda, primarna PCI

Uvod

Primena dvojne antitrombocitna terapije kod pacijenata sa akutnim koronarnim sindromom (AKS) značajno smanjuje ishemijske komplikacije, ali povećava rizik od krvarenja[1]. Čest izvor krvarenja je upravo gastrointestinalni trakt, kako kod bolesnika koji su tretirani konzervativnom terapijom, tako i kod pacijenata koji su lečeni invazivnim metodom (bilo da se radi o primarnoj ili elektivnoj perkutanoj koronarnoj intervenciji – PCI)[2]. Gastrointestinalna krvarenja čine oko 50 % svih spontanih krvarenja koja je javljaju u inicijalnoj fazi AKS, a ova komplikacija značajno pogoršava prognozu kod pacijenata sa AKS. Dokazano je da pacijenti kod kojih se desi ovaj neželjeni događaj imaju povećani ukupni i srčani jednogodišnji mortalitet, kao i incidencu neželjenih događaja kao što su novi infarkt miokarda i neplaniranu revaskularizaciju[3].

Prikaz pacijenta

Bolesnik star 54 godine primljen je u Koronarnu jedinicu (KJ) Urgentnog centra KCS iz sale za kateterizaciju srca nakon primarne PCI u okviru akutnog infarkta miokarda inferiorne lokalizacije. Bolesnik je naveo da je to bila prva prezentacija koronarne bolesti i da je tipičan bol u grudima osetio 3 h pre intervencije. Ostala anamneza po sistemima je bila uredna, bez faktora rizika za krvarenje. Pozvao je službu hitne pomoći koja je slikala EKG na kome je viđena ST elevacija u inferiornim odvodima sa ST depresijom u indirektnim odvodima. Nakon ordinirane dvojne antitrombocitne terapije (Aspirin 300 mg i Klopidogrel 600 mg) transportovan je u salu za kateterizaciju srca KCS. Na koronarografiji je viđena okludirana desna koronarna arterija u koju je implantiran stent. Intervencija je protekla uredno, nakon čega je bolesnik primljen u Koronarnu jedinicu. Pri prijemu u KJ bolesnik je hemodinamski stabilan, kardiopulmonalno kompenzovan i bez bolova u grudima. U daljem toku lečen je dvojnom antitrombocitnom terapijom (Aspirin 100 mg, Klopidogrel 75 mg), beta blokatorom i statinom. U laboratorijskim analizama osim povišenih vrednosti kardiospecifičnih enzima (CKmax-1269 U/L) i lipida (uk. holesterol-6.1 mmol/l, HDL-1.12 mmol/l, LDL -5.1 mmol/l), ostali laboratorijski nalazi su u granicama referentnih vrednosti. Na ultrazvuku srca viđena je leva komora normalne veličine i debljine zidova sa hipo do akinezijom bazalnog segmenta donjeg zida, očuvane ukupne sistolne funkcije, EF 55 %. Trećeg dana hospitalizacije bolesnik povraća taman sadržaj, a u krvnoj slici se registruje pad hemoglobina za 45 g/l (135...90 g/l). Konsultovan je gastroenterolog koji ukida dvojnu antitrombocitnu terapiju i ordinira transfuziju krvi, inhibitore protonske pumpe i parenteralnu nadoknadu tečnosti. Urađena je gastroskopija koja je pokazala difuzni erozivni gastroduodenitis, sa sluznicom pokrivenom fibrinom (u trenutku pregleda nije bilo aktivnog krvarenja). Analiza na antite-

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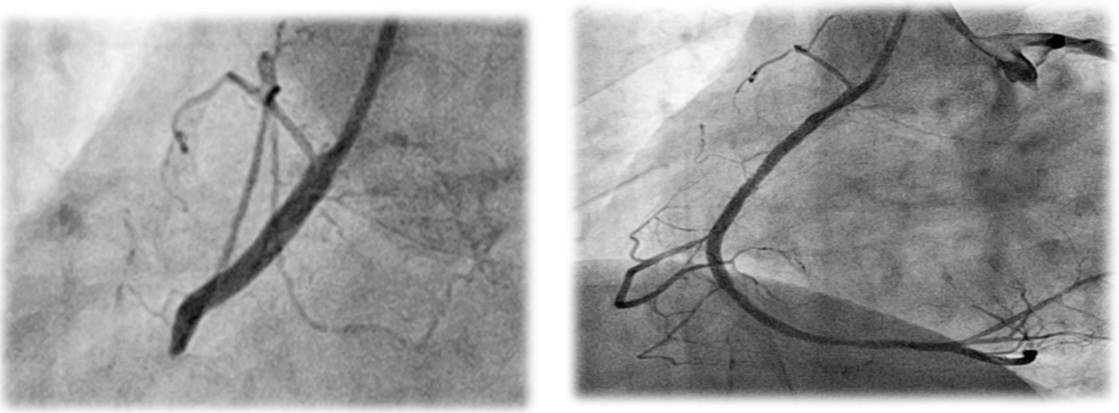
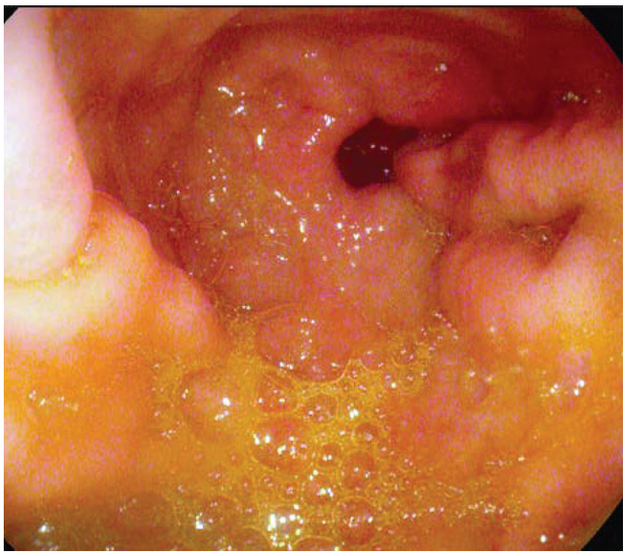


Slika 1. Koronarani angiogram pokazuje infarktnu arteriju (RCA) pre i posle primarne PCI



Slika 2. Erozivni gastritis

la za H.pylori bila je negativna. S obzirom da se krvarenje nije više ponavljalo, od trećeg dana u terapiju je, u dogovoru sa gastroenetrologom, postepeno vraćena antitrombocitna terapija (ASA u acidorezistentnom obliku i klopidogrel, uz blokatore protonske pumpe i preparate gvožđa). Nakon nedelju dana od neželjenog događaja urađena je kontrolna gastroskopija na kojoj je viđena samo blaga hiperemija želudačne i duodenalne sluznice. Bolesnik je 16. dana otpušten kući u stabilnom stanju.

Diskusija

AKS je stresan događaj za organizam koji dovodi, između ostalog, i do smanjenja otpornosti gastrointestinalne sluznice. S druge strane, kod pacijenata sa AKS primenjuje se dvojna antitrombocitna terapija, što je dodatni rizik za krvarenje, te iako tienopiridini ne oštećuju direktno sluznicu, kada se primenjuju u kombinaciji sa aspirinom, povećava se rizik za krvarenje 2–4 puta[4]. Pored toga, osim pacijenata sa već poznatim gastrointestinalnim (GIT) oboljenjima i tegobama, postoji i jedan procenat bolesnika koji imaju klinički neprezentovana, a postojeća GIT oboljenja.

U preporukama za lečenje STEMI iz 2012. godine inhibitori protonske pumpe (IPP) su indikovani u inicijalnoj fazi AKS kod visokorizičnih pacijenata. Markeri visokog rizika za gastrointestinalno krvarenje su: prethodna gastrointestinalna krvarenja, poznata ulkusna bolest, starost preko 65 godina, poznata infekcija H.pylori, istovremena primena kortikosteroida, antikoagulantne terapije i nesteroidnih antiinflamatornih lekova[4]. Kada se gastrointestinalno krvarenje dogodi, produžava se intrahospitalni boravak, mora se ukinuti dvojna antitrombocitna terapija, što povećava rizik od novih ishemijskih događaja, povećava se učestalost komplikacija, kao i mortalitet[3,5,6]. Pored toga, ovim pacijentima je često potrebno dati transfuziju krvi, koja takođe može imati štetna dejstva, povećava mortalitet, učestalost reinfarkta, kao i plućne infekcije. Mehanizam nastanka tih štetnih dejstava je multifaktorijalan i najčešće udružen sa skladištenjem krvi[7,8,9].

Iako je jedno vreme postojala bojazan da istovremena primena pojedinih IPP sa klopidogrelom usporava i smanjuje njegovo antiagregaciono dejstvo[10,11], nove studije su pokazale da nema jasnih dokaza da farmakokinetska interakcija između klopidogrela i IPP ima značajne kliničke posledice[12]. Takođe, pokazano je da nema farmakokinetske interakcije između većine IPP i novih antitrombocitnih lekova[12]. S obzirom da i klopidogrel i IPP imaju kratak poluživot u plazmi (manje od 2 sata), intereakcija ova dva leka može se smanjiti njihovim uzimanjem u različito vreme[13]. Gledano sa ekonomskog stanovišta, krvarenje kao komplikacija kod bolesnika sa akutnim infarktom miokarda značajno podiže cenu lečenja jer, osim što podrazumeva duže bolničko lečenje, vrlo često zahteva i primenu transfuzije krvi, a cena jedne doze transfuzije odgovara ceni 30 kutija pantoprazola.

S obzirom na visok rizik od tromboze stenta kod ranog isključivanja dvojne antiagregacione terapije, potrebna je što brža procena prestanka ili bar smanjenja rizika od krvarenja i postepeno vraćanje antitrombocitne terapije. Raniji stav da je klopidogrel bezbedniji kod bolesnika koji su imali gastrointestinalno krvarenje od aspirina doveden je u pitanje studijama koje su pokazale da tienopiridini usporavaju zarastanje ulkusa suprimiranjem oslobađanja faktora rasta iz trombocita[14]. U kliničkoj studiji Chana i saradnika[14] bolesnici kod kojih je primenjen acidorezistentni oblik aspirina uz IPP imali su značajnije manja rekurentna krvarenja u odnosu na bolesnike koji su primali klopidogrel.

Prikazan je slučaj pacijenta sa AIM lečenog primarnom PCI, bez prethodno postojećih faktora rizika za GIT krva-

renje, kod koga se u ranom intrahospitalnom toku javilo obilno GIT krvarenje koje je zahtevalo primenu transfuzije krvi i privremenu obustavu dvojne antiagregacione terapije. Srećom, pacijent je dobro reagovao na primenjenu terapiju i nije imao nove ishemijske događaje tokom obustave dvojne antiagregacione terapije, kao ni moguće neželjene posledice transfuzije krvi, tako da su jedine posledice bile dužina i cena lečenja.

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Abstract

Gastrointestinal bleeding in a patient with acute myocardial infarction treated with primary percutaneous coronary intervention – case report

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The increasingly prevalent use of antithrombotic drug combination is resulting in growing rates of gastrointestinal bleeding. We decribe a case of 54-years-old patient, admitted to Coronary Care Unit, presented with inferior STEMI. The patient was subsequently found to have acute occlusion of the right coronary artery and was treated with primary percutaneous coronary interventions for RCA. In the beginning he was hemodynamically stable but on third day hematemesis had occured, without any known risk factor for gastrointestinal bleeding. The haemorrhage demanded haemodynamic stabilization, achieved by colloid infusion, blood transfusions and proton pump inhibitors, dual antithrombocite therapy was stopped. Esophagogastroduodenoscopy had shown gastrodudenitis erosiva sangiunans, with mucosa covered with fibrine. Since it was one time event, with gastroenetrologist involved, dual antiplatelet therapy was slowly induced in therapy and on the 16th day the patient was was discharged from hospital in stable state.

Keywords: *gastrointestinal bleeding, acute myocardial infacrtion, primary PCI*

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Prikaz pacijenta

Arterijska hipertenzija i disekcija aorte

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Sažetak

Uvod. Disekcija aorte je hitno stanje u kardiologiji i kardiohirurgiji sa visokim mortalitetom. Najćešći faktor rizika povezan sa disekcijom je arterijska hipertenzija i to uglavnom loše regulisana.

Prikaz slučaja. Bolesnica u 22. godini života i IV mesecu trudnoće hitno hirurški lečena zbog disekcije aorte DeBakey tip I, učinjena intervencija po Bentalu, a drugog postoperativnog dana zbog intrauterine smrti ploda evakuacijona kiretaža. Sada primljena zbog tromboze veštačke aorten valvule, prethodno nekoliko dana nije uzimala antikoagulantnu terapiju. Bolesnik u 57. godini života hitno hirurški lečen zbog disekcije aorte DeBakey tip I, učinjena interpozicija tubus grafta u ascedentnu aortu. Sada primljen zbog neregulisane rezistentne hipertenzije. Pri prijemu u rutinskim analizama ustanovljena hipotireoza sa nemerljivo visokim vrednostima TSH. Započeta supstitucija levotiroksinom.

Zaključak. Disekcija aorte nakon hirurškog lečenja prelazi u hroničnu fazu i zahteva kontinuirano i redovno lekarsko praćenje, adekvatnu regulaciju arterijske hipertenzije i pravovremeno registrovanje mogućih komplikacija.

Ključne reči aneurizma aorte, disekcija aorte, arterijska hipertenzija

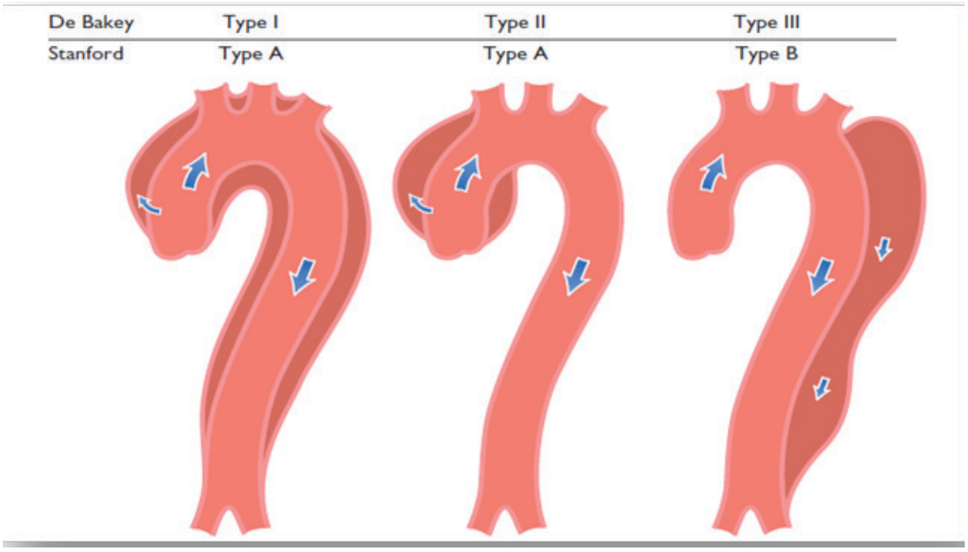
Uvod

Akutni aortni sindromi obuhvataju hitna stanja sa sličnim kliničkim karakteristikama koja zahvataju aortu, a nastaju kada kidanje ili ulceracija intime i medije dozvole prodiranje krvi iz lumena aorte u mediju ili kada ruptura vasa vasorum uzrokuje krvarenje unutar medije. U akutne aortne sindrome spadaju disekcija aorte, intramuralni hematom, penetrirajući aterosklerotski ulkus i traumatska povreda aorte[1].

Najčešći faktor rizika povezan sa disekcijom aorte je arterijska hipertenzija, a sreće se kod 65–75 % bolesnika i uglavnom je loše regulisana. Pored toga, uzročni faktori su prethodne bolesti aorte ili aortne valvule, porodična anamneza za bolesti aorte, ranija kardiohirurška intervencija, pušenje, povreda grudnog koša, intravenska primena narkotika (kokain, amfetamin, i dr)[2].

U kliničkom radu najčešće se koriste DeBakey i Stanford klasifikacija disekcije aorte (Slika 1).

Hirurško lečenje je metoda izbora kod disekcije aorte tip A, ali uprkos napretku u hirurškim i anesteziološkim teh-



Slika 1. Klasifikacija disekcije aorte (Preuzeto: 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases

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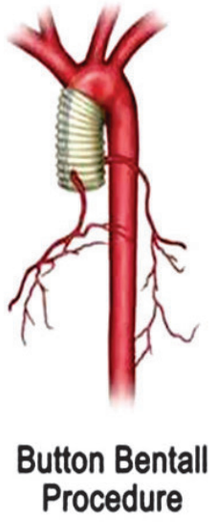
nikama, perioperativni mortalitet je visok (25 %), kao i učestalost neuroloških komplikacija (18 %). Kod neoperisanih bolesnika mortalitet je 50 % u prvih 48 sati (3).

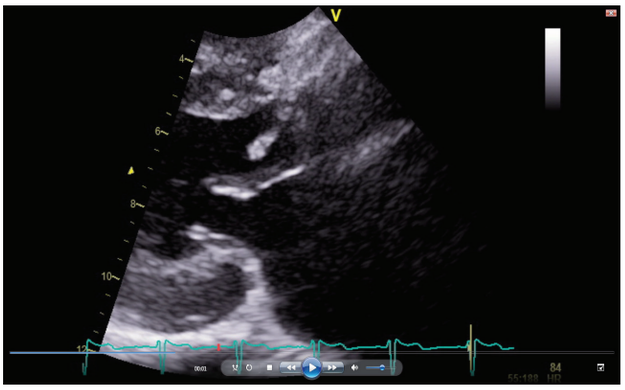
Prikaz bolesnika 1

Bolesnica starosti 28 godina dovežena je u Prijemnu kardiološku ambulantu Instituta za kardiovaskularne bolesti Vojvodine (IKVBV) zbog bolova u grudima i gušenja. Inicijalnim razgovorom sa bolesnicom i pregledom medicinske dokumentacije saznaje se da je 2008. godine operisana na Klinici za kardiohirurgiju IKVBV zbog disekcije aorte DeBakey tip I. Tada je urađena hitna hirurška intervencija po Bentalu – zamena aortnog zaliska, aortnog korena, ascedentne aorte, sa reimplantacijom koronarnih arterija, slika 2. Redovno se kontrolisala od tada. Sada je pet dana pred prijem prestala da uzima antikoagulantnu terapiju.



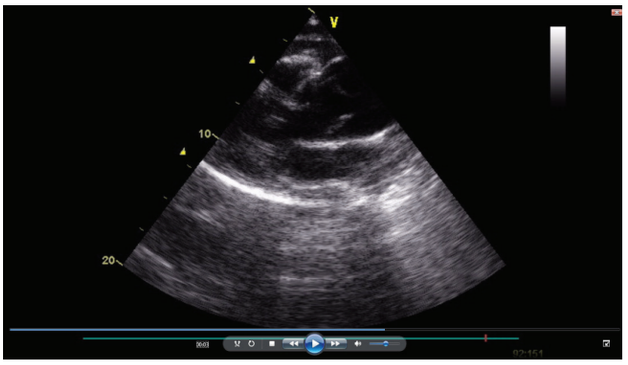
Slika 2. Operacija disekcije ascedentne aorte po Bentalu (Preuzeto sa: https://www.cedars-sinai.edu)

Pri pregledu svesna, komunikativna, afebrilna, lako dispnoična, normotenzivna, tahikardna, kardijalno dekompenzovana (NT-pro-BNP 3359 pg/ml).
Ehokardiografskim pregledom se registruje flotirajuća masa sa komorske strane veštačke aortne valvule (dimenzija 4x13 mm), visok gradijent pritisaka nad veštačkom valvulom (maksimalni 73 mmHg, srednji 46 mmHg), zadeljan perikard, delom imponuje kalcifikovan, sa manjom količinom izliva uz levu komoru, slika 3.



Slika 3. Tromboza veštačke aortne valvule, ehokardiografski pregled

Bolesnica je hitno primljena u Koronarnu jedinicu. Učinjena je sinevalvulografija kojom se uočava malfunkcija veštačkog aortnog zaliska. Na osnovu kliničkih i laboratorijskih nalaza zaključeno je da se radi o trombozi veštačke valvule, isključeno je postojanje endokarditisa. U skladu sa preporukama za lečenje tromboze veštačke valvule, a s obzirom na hemodinamski stabilan klinički status i podatak da je u osnovi hronična disekcija torakoabdominalne aorte, kao i da je hirurška intervencija 2008. godine bila komplikovana infekcijom rane, otežanim zarastanjem i brojnim retrosternalnim priraslicama, u dogovoru sa kardiohirurzima, sprovedeno je medikamentno lečenje, inicijalno intravenskim heparinom. Serijskim ehokardiografskim praćenjem je registrovano postepeno smanjenje gradijenta pritisaka nad veštačkom aortnom valvulom (vrednosti pri otpustu: maksimalni 38 mmHg/srednji 23 mmHg), kao i smanjenje veličine tromba na zalisku. Otpuštena na dalje ambulantno praćenje klinički stabilna.
Inače, od detinjstva se ispituje zbog arterijske hipertenzije. Isključeni su sekundarni uzroci. Ehokardiografskim pregledom u 18. godini opisana dilatirana ascedentna aorta (45 mm), insuficijencija aortnog zaliska II stepena, koncentrična hipertrofija miokarda leve komore (13 mm). Redovno se kontrolisala kod interniste i kardiologa. U 22. godini života prvi put ostaje trudna.
U IV mesecu trudnoće, juna 2008. godine, kolima hitne medicinske pomoći je hitno dovežena u IKVBV, teškog opšteg stanja, hipotenzivna, sa bolom u grudima. Ehokardiografskim pregledom je uočena dilatacija ascedentne aorte (52 mm), sa intimalnim flapom koji se širi u luk aorte, uz značajnu aortnu regurgitaciju, slika 4. Ultrazvučnim pregledom abdomena viđen flap intime i u abdominalnoj aorti. Hitno je operisana, učinjena je intervencija po Bentalu. Drugog postoperativnog dana je zbog intrauterine smrti ploda učinjena evakuacijona kiretaža.

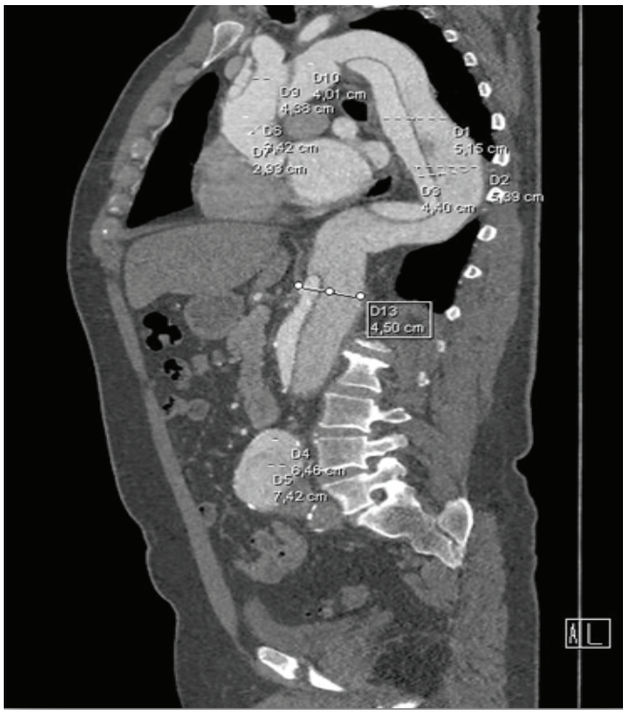


Slika 4. Disekcija ascedentne aorte, ehokardiografski pregled

Patohistološki nalaz na aorti: cistična medionekroza aorte, miksomatozna degeneracija zalistaka.
Bolesnica je uspešno oporavljena i u daljem toku hospitalizacije bez komplikacija. Redovno se kontrolisala kod interniste, kardiologa i kardiohirurga. Pri svakom pregledu vođeni razgovori o potencijalnom veoma visokom riziku za neželjene događaje u slučaju ponovne trudnoće. Insistirano na optimalnom antihipertenzivnom lečenju, adekvatnoj tromboprofilaksi.

Prikaz bolesnika 2

Bolesnik starosti 63 godine dovežen je u IKVBV zbog bola u leđima i stomaku. Inače, radi se o bolesniku koji je 6 godina ranije lečen zbog disekcije aorte DeBakey tip I kada je učinjena hitna kardiohirurška operacija, interpozicija tubus grafta dužine 10 cm u ascedentnu aortu. Otpušten sa 4 antihipertenzivna leka, zadovoljavajuće regulisanog arterijskog pritiska. Kontrolisao se ambulantno u nadležnoj ustanovi kod izabranog lekara. U međuvremenu jednom pregledan kao hitan u IKVBV zbog neregulisane arterijske hipertenzije.
Sada je pri pregledu hipertenzivan, ritmičan, bradikardan, kardijalno kompenzovan. CT pregledom aorte su opisani znaci hronične disekcije torakoabdominalne aorte, sa dominacijom lažnog lumena u kome se formiraju parijetalne trombotične mase. Graft u ascedentnoj aorti održanog lumena. Velike grane luka aorte polaze iz pravog lumena, kao i grane za trbušne organe i desni bubreg, dok leva bubrežna arterija polazi iz lažnog lumena, a izostaje opacifikacija levog bubrega tokom pregleda, slika 5.



Slika 5. Disekcija torakoabdominalne aorte, CT angiografija

U laboratorijskim nalazima kod bolesnika ne registruju se znaci bubrežne insuficijencije, ali se registruju snižene vrednosti hormona štitaste žlezde (FT3 2,11 pmol/l (4–8,3), FT4 5,60 pmol/l (9–20)), uz nemerljivo visok TSH > 60 µUI/ml (0,25–5,0). Po preporuci endokrinologa, odmah je započeto supstituciono lečenje levotiroksinom. Kod bolesnika se postepeno tokom hospitalizacije uz primenu 4–5 antihipertenzivnih lekova uspeva postepeno regulisati arterijska hipertenzija.
Otpušten je normotenzivan, bez subjektivnih tegoba. Sa preporukom za redovno lečenje i praćenje od strane endokrinologa, kardiologa i kardiohirurga.

Diskusija

Navedeni pacijenti su primeri uspešnog lečenja akutne disekcije aorte DeBakey tip I, ali u oba slučaja smo želeli da istaknemo da je operacija akutne disekcije aorte zapravo samo jedan kratkotrajan segment dugotrajnog i pažljivog lečenja i praćenja bolesnika sa oboljenjima aorte.
U oba slučaja ističe se važnost kontrole i regulacije arterijske hipertenzije. U prvom prikazu postavlja se pitanje optimalnog lečenja arterijske hipertenzije u trudnoći, kao i postupanje po pitanju dilatacije ascedentne aorte i pre planirane trudnoće.
Arterijskom hipertenzijom u trudnoći smatra se krvni pritisak ≥ 140 mmHg sistolni i ≥ 90 mmHg dijastolni. Većina trudnica sa arterijskom hipertenzijom pre trudnoće tokom trudnoće ima blagu do umerenu arterijsku hipertenziju i nizak rizik za neželjene kardiovaskularne događaje. Kod nekih trudnica se čak zbog fiziološkog pada arterijskog pritiska tokom prvog trimestra antihipertenzivna terapija u ovom periodu može izostaviti, ali to zahteva strogo praćenje i ponovno uvođenje terapije ukoliko je potrebno[4].
Kod naše bolesnice upravo je ova fiziološka pojava bila razlog da se verovatno tokom prvog trimestra redukuje primena antihipertenziva, a sve u cilju izbegavanja nepovoljnih efekata lekova na razvoj ploda. Disekcija aorte se dogodila upravo nakon ovog perioda, početkom drugog trimestra.
Druga dilema koja je kod ove bolesnice nužan predmet diskusije je prethodno prisutna dilatacija ascedentne aorte. U vodiču za lečenje aneurizme ascedentne aorte Evropskog kardiološkog udruženja iz 2014. godine preporučuje se hirurško lečenje aneurizme ako je njen dijametar ≥ 45 mm kod osoba sa Marfanovim sindromom, ≥ 50 mm kod osoba sa bikuspidnom valvulom, ≥ 55 mm kod osoba bez elastopatija (IIa C). Ali se takođe navodi i da se manji dijametri mogu uzeti u obzir zavisno od konstitucije tela, visine rasta, progresije aneurizme, aortne regurgitacije, planirane trudnoće (IIb C)[1].
U preglednom članku Immera i saradnika navode se fiziološki događaji u trudnoći koji doprinose povećanju rizika za disekciju aorte, naročito kod prethodno poznatih elastopatija. Tokom trudnoće raste srčana frekvenca, udarni volumen, masa miokarda leve komore i enddijastolni volumen. Ove pojave su naročito izražene u trećem trimestru, te je tada i rizik za disekciju najveći. Takođe se ističu promene u strukturi vezivnih vlakana pod dejstvom hormona tokom trudnoće, što naročito dobija značaj kod osoba sa prethodno prisutnim elastopatijama. Autori zaključuju da se kod žena kod kojih je prečnik korena aorte > 40 mm ili manje u slučaju sitnije telesne konstitucije, uz prisutan Marfanov sindrom ili bikuspidnu valvulu, preporučuje razmotriti hirurško lečenje aneurizme aorte pre trudnoće[5].
Bolesnici koji su preživeli akutnu disekciju aorte ulaze u hroničan tok bolesti koji može biti stabilan i bez komplikacija, ali se može komplikovati progresijom aneurizme, hroničnom malperfuzijom organa i ekstremiteta, rekurentnim bolom ili rupturom. Nakon hirurškog lečenja disekcije tip A zaostaje disekcija descedentne i abdominalne aorte sa svim gore navedenim mogućim kompli-

kacijama. Stoga je praćenje i adekvatno lečenje ovih bolesnika veoma važno. Oba bolesnika koja smo prikazali imaju hroničnu disekciju torakoabdominalne aorte nakon operacije disekcije DeBakey tip 1 i zahtevaju redovno kliničko i imidžing praćenje i strogu kontrolu arterijskog pritiska. CT je metoda izbora i preporučuje se u godišnjim intervalima nakon hirurškog lečenja ili endovaskularne rekonstrukcije aorte. Redovno kliničko praćenje je neophodno, nešto češće u prvoj godini nakon dijagnoze ili intervencije, a potom u jednogodišnjim intervalima[1]. Potrebna je stroga kontrola arterijskog pritiska, naročito zbog toga što > 50 % ovih bolesnika ima rezistentnu hipertenziju. Preporučuje se da arterijski pritisak bude < 130/80 mmHg[6].

Zaključak

Lečenje disekcije aorte zahteva multidisplinarni pristup, kako u akutnoj tako i u hroničnoj fazi. Redovno kliničko praćenje bolesnika u hroničnoj fazi bolesti, kao i nakon operacije veoma je važno zbog mogućih komplikacija. Potrebna je stroga kontrola i regulacija krvnog pritiska.

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Abstract

Arterial hypertension and aortic dissection

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Background. *Aortic dissection is a emergency in cardiology and cardiac surgery with high mortality. The most common risk factor associated with aortic dissection is arterial hypertension which is mainly poorly regulated.*

Case report. *Female, 22 years old in IV month of pregnancy underwent emergency cardiac surgery because of aortic dissection DeBakey type I, Bentall intervention, and on the second postoperative day due to intrauterine fetal death underwent evacuation curettage. Six years later was hospitalized because of thrombosis artificial aortic valve, the past few days was not taking anticoagulant therapy. Male, 57 years old, underwent emergency cardiac surgery because of aortic dissection DeBakey type I, interposition tube graft to the ascending aorta. Six years later was hospitalized due to unregulated resistant hypertension. On admission in the routine laboratory tests hypothyroidism was determined with TSH immeasurably high. Levothyroxine substitution was started.*

Conclusion. *Chronic dissection of descending and abdominal aorta mainly persist after surgery and requires continuous and regular medical monitoring, adequate arterial hypertension regulation and detecting possible complications.*

Keywords: *Aortic aneurysm, Aortic dissection, Arterial hypertension*

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Prikaz pacijenta

Asimptomatska tesna aortna stenoza i test opterećenjem

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Sažetak Prikazujemo asimptomatičnog pacijenta sa bivelarnom aortnom stenozom koji je upućen na procenu težine aortne stenoze putem funkcionalnog testiranja i određivanja dalje terapije.

Ključne reči asimptomatska aortna stenoza, test opterećenja

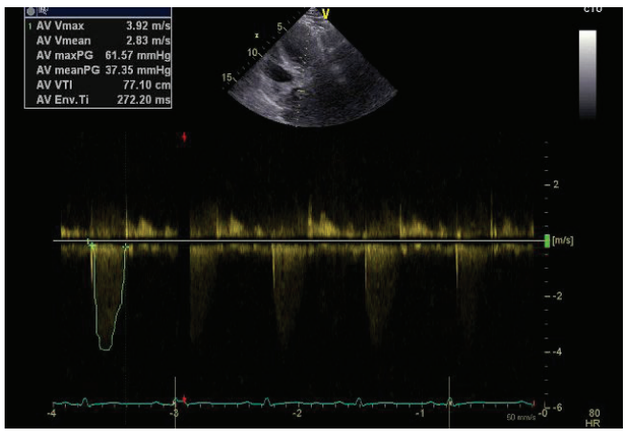
Uvod

Aortna stenoza (AS) je najčešća valvularna bolest srca[1,2]. I dok je kod pacijenata sa tesnom simptomatskom AS indikovana hirurška zamena aortnog zaliska, ili eventualno perkutana zamena kao alternativa[1,2], i dalje nema konsenzusa, ali ni jasnih dokaza oko lečenja pacijenata sa tesnom, hemodinamski značajnom, asimptomatskom AS. Ipak, najnovije ESC preporuke[1] i publikovane studije[3–5] nam ukazuju da klasičan test opterećenja, ili dobutaminski test kao alternativa, ima mesta u dijagnostici i odluci o operativnom lečenju kod ovih pacijenata. Ovo je posebno važno kod osoba sedentarnog načina života kod kojih nismo sigurni da li postoje simptomi uzrokovani AS, bez obzira što ih sam pacijent negira.

Prikazujemo slučaj asimptomatskog pacijenta sa bivelarnom AS upućenog iz regionalnog zdravstvenog centra radi procene težine AS i određivanja dalje terapije.

Prikaz pacijenta

Muškarac star 36 godina, nezaposlen i slabo fizički aktivan, upućen je u našu ustanovu radi procene težine AS i određivanja daljeg načina lečenja. Pacijent od detinjstva zna za šum na srcu, a eho srca rađen 10 meseci pre našeg pregleda u regionalnom zdravstvenom centru ukazao je na postojanje umerene AS sa maksimalnom brzinom protoka (V_{max}) preko aortnog ušća 3,7m/s i maksimalnog gradijenta od 57,8 mmHg. Ehokardiografski pregled u miru u našoj ustanovi u položaju levog dekubitusa iz apikalnog preseka pet šupljina pokazao je postojanje umerene AS (Slika 1), međutim iz desnog parasternalnog preseka dobijeni su značajno veći gradijenti koji su upućivali na postojenje tesne aortne stenoze (površina aortnog ušća bila je 0.91 cm^2, slika 2). Sistolna funkcija leve komore bila je normalna (EF 77,6 %) i sve dimenzije srčanih šupljina su bile u granicama normale. Ehokardiografski je utvrđeno postojanje bikuspidne aortne valvule. S obzirom na slabu fizičku aktivnost pacijenta, odlučili smo se da uradimo test fizičkim opterećenjem (TFO) kako bismo sa sigurnošću odredili ono



Slika 1. Prikaz VTI preko aortnog ušća iz položaja levog dekubitusa, apikalni presek pet šupljina

što je najvažnije kod pacijenata sa tesnom AS, a to je odgovor na pitanje da li postoje simptomi uzrokovani samom AS. Test fizičkim opterećenjem je urađen na poluležećem ergobiciklu po R15 protokolu[6]. Urađen je maksimalan test[1] s obzirom da je u toku testa dostignuto 84 % maksimalne predviđene frekvence srca za pacijentove godine i pol, a sam test je prekinut pri opterećenju od 133W (65 % predviđenog opterećenja, slika 3) zbog zamora u nogama i nemogućnosti pacijenta da dalje okreće pedale. Sve vreme testa, kao i po prekidu testa pacijent je bio bez tegoba karakterističnih za AS (dispnea, stezanje u grudima, vrtoglavica-nesvestica), dakle, test je bio asimptomatski. Sinhrono sa testom pacijent je ehokardiografski praćen, a na kraju testa je zabeležen značajan porast u V_{max}, kao i u maksimalnom i srednjem gradijentu preko aortnog ušća (slika 4). Dakle, srednji gradijent je porastao za gotovo 40 mmHg tokom opterećenja. Nakon završenog testa bilo je jasno da se radi o asimptomatskoj, vrlo tesnoj AS. Sada se postavilo pitanje šta dalje sa ovim pacijentom, da li mu preporučiti zamenu aortnog zaliska ili ga i dalje pratiti, i ako bi se odlučili za opciju praćenja, za koliko vremena mu zakazati kontrolu.

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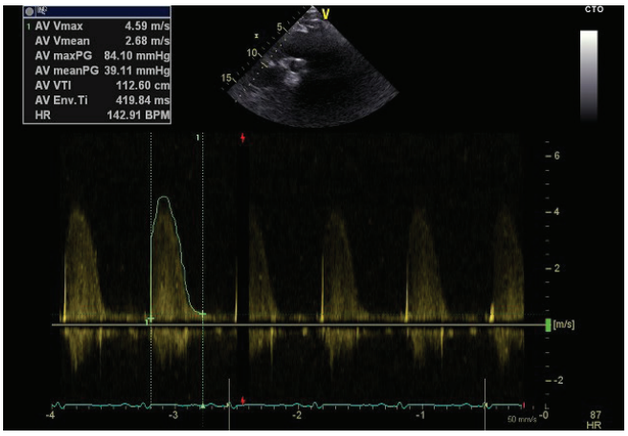
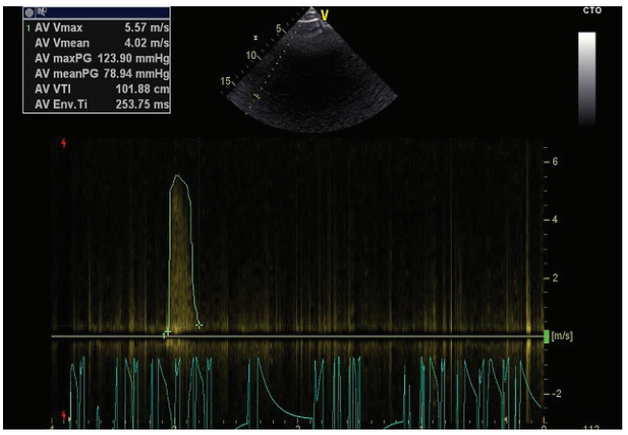


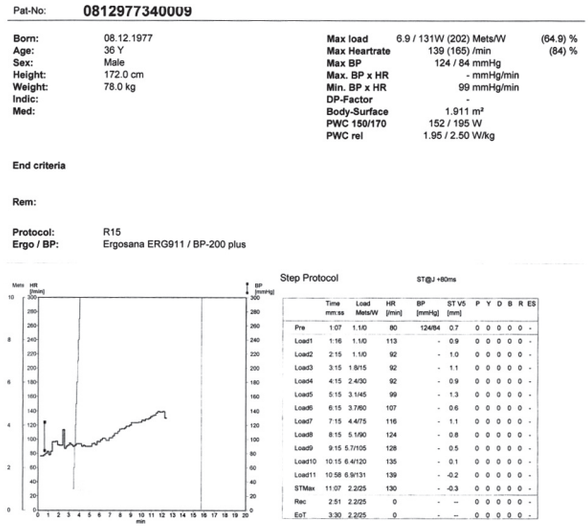
Slika 2. Prikaz VTI preko aortnog ušća i maksimalne brzine protoka u miru dobijene iz desnog parasternalnog preseka



Slika 4. Prikaz VTI preko aortnog ušća i maksimalne brzine protoka dobijene na kraju testa

Diskusija

U odgovoru na poslednje pitanje konsultovali smo najnovije ESC preporuke[1]. U konkretnom slučaju (asimptomatski pacijenti sa porastom srednjeg gradijenta tokom testa ≥ 20 mmHg) ESC preporuke kažu da se pacijentu može preporučiti zamena aortnog zaliska (preporuka IIb, nivo dokaza C), ali da je donekle realnija opcija odlučiti se za praćenje. Dakle, obe opcije su prema ESC preporukama prihvatljive. Ipak, važno je napomenuti da se prognoza pacijenata sa AS značajno pogoršava sa pojavom simptoma (prosečno preživljavanje u tom slučaju je manje od 2 godine[3], a preporučeno vreme od pojave simptoma do hirurške zamene aortnog zaliska je ≤ 3 meseca). Stoga je preporučeno vreme za kontrolni pregled ovakvih pacijenata 3–6 meseci, i to ne zato da bismo opet ehokardiografski procenjivali AS, nego da bismo na vreme uočili pojavu simptoma. Naravno, u slučaju da smo se odlučili da pacijentu predložimo da dođe na kontrolni pregled, moramo ga upoznati sa najčešćim/klasičnim simptomima uzrokovanim AS (nedostatak vazduha, anginozne tegobe, vrtoglavice, nesvestice, gubitak svesti), te da mu naglasimo da se u slučaju pojave nekog od pomenutih simptoma odmah javi ordinirajućem kardiologu. U našem slučaju, imajući u vidu godine pacijenta, postignut nešto slabiji funkcionali kapacitet i realno stanje da se u Srbiji na zamenu aortnog zaliska čeka duže od 3 meseca, pacijentu smo predložili zamenu aortnog zaliska. Pacijent je to odbio, tako da smo mu sledeću kontrolu zakazali za 6 meseci, uz sugerisanje da obrati pažnju na pojavu simptoma i izbegavanje velikih fizičkih opterećenja, naročito podizanje tereta, a u slučaju pojave nekog od pomenutih simptoma da se odmah javi svom nadležnom kardiologu.



Slika 3. Prikaz dostignutog opterećenja i maksimalne postignute frekvence tokom testa

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Abstract

Asymptomatic severe aortic stenosis and stress testing

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We present an asymptomatic patients with bivelar aortic stenosis refered for evaluation of severitz of aortic stenosis with stress testing and future therapy.

Keywords: *asymptomatic aortic stenosis, stress testing*

Srce i krvni sudovi 2014; 33(4):241-245

Prikaz pacijenta

Lečenje arterijske hipertenzije u svetlu novih preporuka

Bojan Ilić[1], Milovan Stojanović[1], Marina Deljanin Ilić[1,2]

[1]Institut za lečenje i rehabilitaciju Niška Banja, [2]Medicinski fakultet, Univerzitet u Nišu

Sažetak Predstavljamo pacijentkinju koja je primljena sa simptomima i hipertenzije, nepravilnog srčanog rada po tipu apsolutne aritmije i srčane slabosti.

Ključne reči srčana insuficijancija, atrijalna fibrilacija, arterijska hipertenzija

Uvod

Hipertenzija predstavlja veliki nezavisni faktor rizika za nastanak kardiovaskularnih oboljenja[1,2]. Smatra se da u svetu trenutno od povišenih vrednosti krvnog pritiska boluje 30–45 % ljudi[3]. Incidenca hipertoničara se povećava sa uzrastom pri čemu 3/4 obolelih starijih od 75 godina boluje od sistolne hipertenzije[4]. Hipertenzija, takođe, pretstavlja nezavisni faktor rizika za nastanak atrijalne fibrilacije (AF), pri čemu je ovaj poremećaj srčanog ritma najčešći pri otpustu pacijenata iz bolnice[5]. Veoma je bitna regulacija krvnog pritiska kod pacijanata sa AF koji uzimaju antikoagulantnu terapiju jer neregulisane vrednosti lakše mogu dovesti do intrakranijalnog krvarenja[6].

Sa druge strane, postoji jasna korelacija između srčane slabosti i neregulisanog krvnog pritiska[7]. Regulacija krvnog pritiska u takvih pacijenata smanjuje rizik od komplikacija i produžava život. Takođe, poznato je da atrijalna fibrilacija može direktno uzrokovati srčanu insuficijenciju jer uzrokuje deficit dijastolnog punjenja nastalog usled tahikardije i smanjenog komorskog punjenja krvlju[8,9]. Iz svega navedenog jasno je da terapijski pristup pacijentu koji boluje od srčane slabosti, hipertenzije i atrijalne fibrilacije mora biti kompleksan i sveobuhvatan. U tome nam mogu pomoći vodiči dobre kliničke prakse, ali nikako ne treba smetnuti sa uma da preporuke treba znati, ali uvek treba imati individualni pristup svakom bolesniku ponaosob.

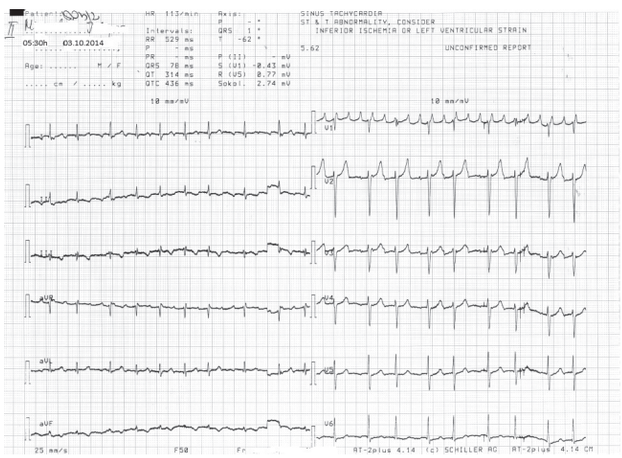
Prikaz pacijenta

Bolesnica J. M. 1934. godište iz Niške Banje, primljena u Koronarnu jedinicu Klinike za kardiologiju Instituta za lečenje i rehabilitaciju Niška Banja zbog gušenja, povišenih vrednosti krvnog pritiska i osećaja ubrzanog i nepravilnog srčanog rada, a pod dijagnozom dekompenzovane srčane slabosti (na osnovu kliničkog pregleda, BNP, rendgengrafije pluća i ultrazvuka srca). Iz anamneze se dobija podatak da pacijentkinja unazad mesec dana oseća zamor pri najmanjem naporu. Navodi da do sada nije bila ispitivana i lečena zbog srca. Od faktora rizika za ishemijsku bolest srca navodi visoke vrednosti krvnog pritiska unazad 25 godina, povišene vrednosti masnih materija u krvi i gojaznost. Za nepravilan srčani rad zna godinu dana. Navodi da joj je lekar opšte prakse uključio aspirin u terapiju uz usmeni predlog za antikoagulantnu terapiju.

Fizikalni pregled: Na prijemu bolesnica svesna, orjentisana, dispnoična, ortopnoična, srednje razvijena, gojazna, kože i vidljivih sluzokoža bleđe prebojenih, zauzima polusedeći položaj. Auskultacijom na plućima oslabljeno disanje sa zastojnim promenama u donjoj trećini plućnih polja. Na srcu akcija aritmična po tipu apsolute, SF oko 114/min., sistolni regurgitacioni šum 3/6 nad iktusom. Na prijemu TA 180/90 mmHg. Jetra i slezina se ne palpiraju. Na potkolenicama diskretni pretibijalni edemi, bez deformiteta i varikoziteta.

Po prijemu napravljen plan ispitivanja bolesnice koji je obuhvatao EKG, laboratoriju, rendgengrafiju pluća i srca, 24 h ambulatorni monitoring krvnog pritiska, 24 h holter monitoring EKG-a, ultrazvučni pregled srca, dopler krvnih sudova vrata.

EKG nalaz: atrijalna fibrilacija sa apsolutom komora (fluter pretkomora sa promenljivim sprovođenjem 2–3:1), SF oko 114/min. (Slika 1)



Slika 1. Elektrokardiografija na prijemu

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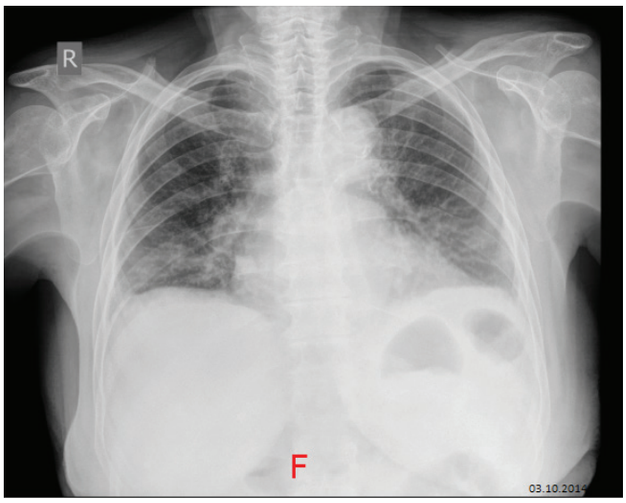
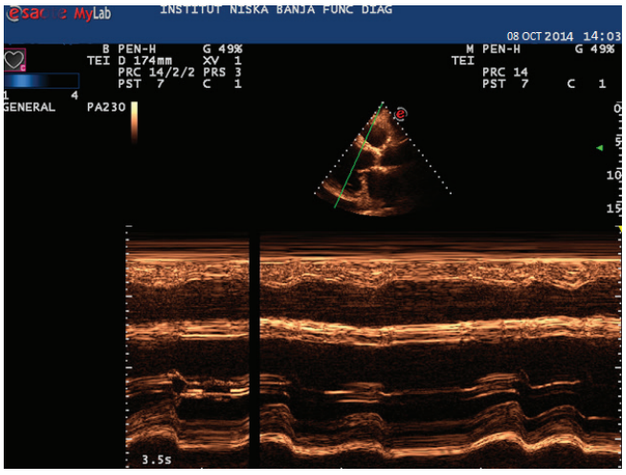
Laboratorija: Holesterol 7.3 mmol/l (HDL 0.9 mmol/l, LDL 5.4 mmol/l), trigliceridi 2.0 mmol/l, glikemija 5.8 mmol/l, kreatinin 110.46 mmol/l, ureja 8.8 mmol/l, K+ 4.2 mmol/l, Na+ 147 mmol/l, BNP 364 pg/ml, TnI<0.1 mmol/l, leukociti 9.9 G/L, RBC 4.44 T/L, hemoglobin 122 g/L, HCT 0.3 L/L, trombociti 154 G/L, sedimentacija 20 mm/h, BMI 28.34, GFR 41 ml/min/1.73m².
Rtg pluća i srca: znaci srčanog zastoja uz uvećanu srčanu senku (Slika 2)



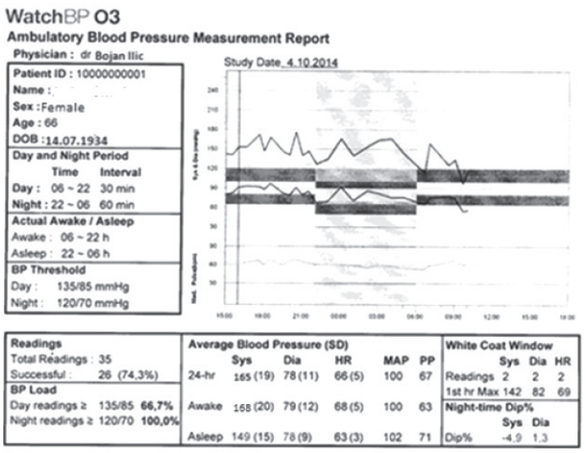
Slika 2. Rendgengrafija pluća i srca

Ultrazvučni pregled srca: EF 45 %, hipokinezija septuma, LA 45 mm, MR 2+, TR 2+, SPDK 40 mmHg (Slika 3)



Slika 3. Ehokardiografija na prijemu (M-mod, uzdužni parasternalni presek)

24 h holter EKG-a: U toku 22:14 h praćenja EKG-a resgitrovano je 110489 otkucaja srca. Sve vreme fibrilacija pretkomora sa apsolutom komora, min. SF 48/min., max. SF 126/min., uz prosečnu SF 85/min. Nisu registrovane pauze u srčanom radu. Zabeležene su 52 pojedinačne, uniformne VES. Bez dinamike na ST segmentu i T talasu.
Dopler krvnih sudova vrata: Desno u proksimalnom segmentu ACI fibrokalcifikovan plak 45 %. Levo u ishodišnom segmentu ACI fibrokalcifikovan plak 32 %.
24 h ambulatorni monitoring krvnog pritiska: Narušenog cirkadijalnog ritma uz prosečne vrednosti krvnog pritiska 165/78 mmHg. (Slika 4)

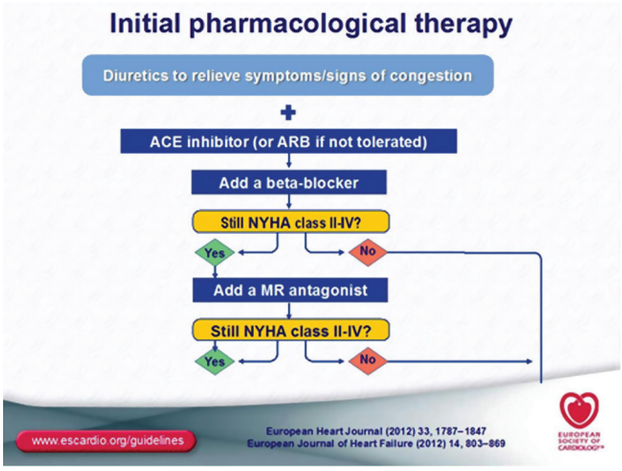


Slika 4. 24 h monitoring krvnog pritiska

Terapija na prijemu: Atenolol 50 mg, Ramipril 2.5 mg, Hidrochlortazid 12.5 mg, Aspirin 100 mg, Simvastatin 10 mg.
Bolesnica je otpuštena iz bolnice sa dijagnozom kongestivne srčane insuficijencije, arterijske hipertenzije, aritmije apsolute, hiperlipidemije i bilateralne stenoze unutrašnjih karotidnih arterija uz predlog da za mesec dana uradi kontrolni ambulatorni monitoring krvnog pritiska – odrađen uz uredan cirkadijalni ritam i prosečne vrednosti krvnog pritiska (slika 5), kao i stres ehokardiografski test radi odlučivanja o daljem načinu lečenja. Terapija na otpustu: Dilacor 0.25 mg, Bisoprolol 5 mg, Perindopril 5 mg, Amlodipin 5 mg, Furosemid 20 mg, Spironolactone 25 mg, Farin po INR-u, Atorvaststin 20 mg uveče, Spray NTG po potrebi.

Diskusija

Smatra se da 1–2 % svetske populacije boluje od srčane insuficijencije. Pri tome treba imati na umu da procenat obolelih raste sa uzrastom, pa se tako pretpostavlja da više od 10 % svetske populacije starije od 70 godina boluje od srčane slabosti[6]. Obično takvi bolesnici imaju komorbiditete koji pogoršavaju stanje srčane slabosti kao što su hipertenzija, atrijalna fibrilacija, bubrežna insuficijencija, itd. Zbog toga terapijski pristup takvim bolesnicima mora biti sveobuhvatan. Prema najnovijim preporukama Evropske asocijacije kardiologa stanje srčane insuficijancije zahteva primenu diuretika, beta blokatora, ACE inhibitora ili AT1 blokatora kao i/ili primenu antagonista aldosterona (slika 5; tabela 1)[9]. Svi ovi lekovi su i u preporukama za lečenje povišenog krvnog pritiska.
Lek izbora kod pacijenata sa srčanom insuficijencijom je inhibitor angiotenzin konvertujućeg enzima (ACE inhibitori). Brojne studije su dokazale blagotvorni efekat ACE inhibitora na remodelovanje leve komore u pacijenata koji boluju od srčane insuficijencije.[11–16]. Pogotovo je nezamenjiva njihova uloga koda pacijenata satrije životne dobi. Upotreba perindoprila u starijih pacijenata sa srčanom slabošću pokazala je njegov pozitivan efekat na redukciju kardiovaskularnog mortaliteta i broj rehospitalizacija[17]. Takođe, dokazan je izvrstan efekat perindoprila u regulaciji krvnog pritiska kod pacijenata starije životne dobi[18].
Primena beta blokatora imala je višestruki efekat kod naše bolesnice. Naime, u velikim studijama dokazan je



Slika 5. Inicijalna terapija u srčanoj slabosti

blagotvorni efekat pojedinih BB (karvedilol, metoprolol sukcinat, bisoprolol i binevol), u prvom redu bisoprolola[19], u smanjivanju kardiovakularnog mortaliteta i morbiditeta pacijenata koji boluju od srčane insuficijencije[20–23], što se mahom pripisuje njihovom antiishemijskom efektu, kao i pozitivnom uticaju na ejekcionu frakciju. S druge strane, upotreba atenolola je povezana sa povećanjem mortaliteta i morbiditeta[24]. Tako da je atenolol zamenjen bisoprololom.

Upotreba antagonista aldosterona u srčanoj insuficijenciji je ispitivana u velikim studijama RALES (spironolactone) i EMPHASIS-HF (eplerenon)[25,26]. Obe studije su dokazale da upotreba antagonista aldosetrona smanjuje kardiovaskularni mortalitet, kao i broj rehospitalizacija pacijenata sa srčanom insuficijencijom povezujući to sa pozitivnim efektom koji antagonisti aldosterona imaju na redukciju procesa remodelovanja srca.

Studija koja je upoređivala upotrebu oralnih antikoagulanasa (OAK) i aspirina u prevenciji moždanog udara kod pacijenata sa atrijalnom fibrilacijom pokazala je inferiornost acetil-salicilne kiseline u odnosu na vitamin K antagoniste[27]. Evropska asocijacija kardiologa preporučuje izračunavanje CHA_2DS_2-VASc i HAS-BLED skora pre uvođenja antikoagulantne terapije (tabele 2, 3). Kako je naša bolesnica imala skor – 7 na CHA_2DS_2-VASc skali odlučili smo se za uvođenje OAK sa ciljem prevencije moždanog udara. S druge strane, zbog velikog rizika od krvarenja HAS–BLED skor – 3, bolesnici je isključen aspirin.

Risk factor-based point-based scoring system - CHA_2DS_2-VASc

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥ 75 ans	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease*	1
Age 65-74	1
Sex category [i.e. femal sex]	1
Maximum score	**9**

Tabela 2. Tabela rizika za uzimanje antikoagulantne terapije

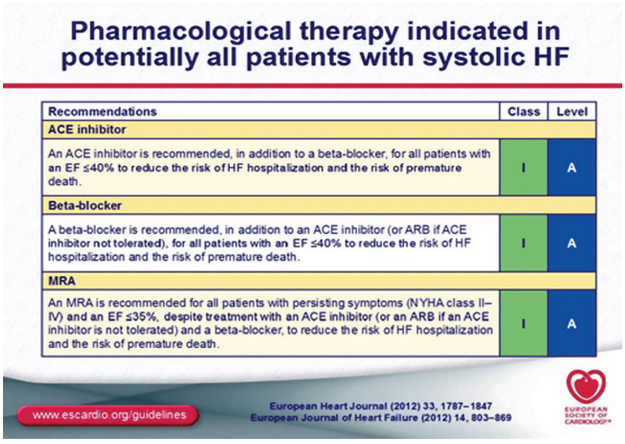


Tabela 1. Terapija u srčanoj slabosti

Upotrebom diuretika henelove petlje (furosemid) stimulisali smo venodilataciju i diurezu koja je dovela do regresije gušenja, pretibijalnih edema i zastoja na plućima dok je upotreba statina bila uzrokovana visokim vrednostima lipidnih materija u krvi (simvastatin zamennjen atorvastatinom), promenama na karotidama i najverovatnije postojanje koronarne bolesti u osnovi srčane slabosti.

Na ambulatornom monitoringu rađenom neposredno pre otpusta iz bolesnice registrovan je narušeni cirkadijalni ritam sa prosečnom vrednošću 165/78 mmHg. Kako je preporučena vrednost sistolnog KP za starije od 80 godina 140–150 mmHg (tabela 4), postavilo se pitanje da li povećati vrednost ACE inhibitora ili u terapiju uvesti novi lek. Uvođenje novog leka pravdamo velikom meta-analizom koja je pokazala da je kombinacija dva različita antihipertenzivna leka pet puta efikasnija nego dupliranje doze jednog leka[28]. Evropska asocijacija kao lekove izbora za sistolnu hipertenziju preporučuje kalcijum antagoniste ili diuretike. Mi smo se odlučili za Ca antagonist- amlodipin koji je lek izbora u izolovanoj sistolnoj hipertenziji, ali kod bolesnika sa postojećom srčanom

HAS-BLED	
Hypertension (systolic blood pressure >160 mmHg)	1
Abnormal renal and liver function (1 point each)	1 or 2
Stroke	1
Bleeding tendency or predisposition	1
Labile international normalized ratio (if on warfarin)	1
Elderly (e.g. age > 65 years)	1
Drugs (e.g. concomitant aspirin, NSAID) or alcohol (1 point each)	1 or 2
Maximum score	9
A HAS-BLED score ≥3 suggests that caution is warranted when prescribing oral anticoagulation and regular review is recommended.	

HAS-BLED = Hypertension, Abnormal renal/liver function (1 point each), Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65), Drugs/alcohol concomitantly (1 point each); NSAID = non-steroidal anti-inflammatory drug.

Tabela 3. Rizik od krvarenja po HAS-BLED skoru

Elderly

Recommendations	Class	Level
In elderly hypertensives with SBP ≥160 mmHg there is solid evidence to recommend reducing SBP to between 150 and 140 mmHg.	I	A
In fit elderly patients <80 years old antihypertensive treatment may be considered at SBP values ≥140 mmHg with a target SBP <140 mmHg if treatment is well tolerated.	IIb	C
In individuals older than 80 years with an initial SBP ≥160 mmHg it is recommended to reduce SBP to between 150 and 140 mmHg, provided they are in good physical and mental conditions.	I	B
In frail elderly patients, it is recommended to leave decisions on anti-hypertensive therapy to the treating physician, and based on monitoring of the clinical effects of treatment.	I	C
Continuation of well-tolerated antihypertensive treatment should be considered when a treated individual becomes octogenarian.	IIa	C
All hypertensive agents are recommended and can be used in the elderly, although diuretics and calcium antagonists may be preferred in isolated systolic hypertension.	I	A

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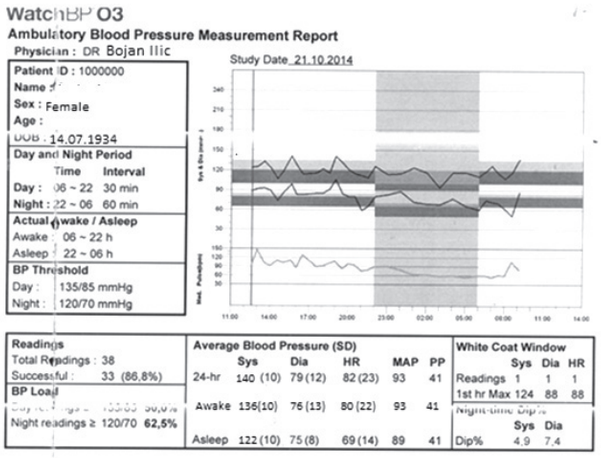
Eur Heart J, 2013; 34: 2159-2219
J Hypertens, 2013; 31: 1281-1357
Blood Pressure, 2013: 193-278

European Society of Hypertension

Tabela 4. Preporuke vrednosti krvnog pritiska kod starijih



Slika 6. 24h Monitoring krvnog pritiska

slabošću (tabela 5). Na kontrolnom ambulatornom monitoringu KP rađenom dve nedelje nakon otpusta prosečna vrednost iznosila je 140/79 mmHg (slika 6). Ove vrednosti krvnog pritiska odgovaraju samoj bolesnici, a u potpunosti su u skladu sa preporukama za lečenje arterijske hipertenzije.

Recommendations for the treatment of hypertension in patients with symptomatic HF (NYHA functional class II–IV) and LV systolic dysfunction

Recommendations	Class[a]	Level[b]	Ref[c]
Step 1			
One or more of an ACE inhibitor (or ARB), beta-blocker, and MRA is recommended as first-, second-, and third-line therapy, respectively, because of their associated benefits (reducing the risk of HF hospitalization and reducing the risk of premature death).	I	A	87, 108–111
Step 2			
A thiazide diuretic (or if the patient is treated with a thiazide diuretic, switching to a loop diuretic) is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), beta-blocker, and MRA.	I	C	–
Step 3			
Amlodipine is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), beta-blocker, MRA, and diuretic.	I	A	188, 189
Hydralazine is recommended when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), beta-blocker, MRA, and diuretic.	I	A	114–116
Felodipine should be considered when hypertension persists despite treatment with a combination of as many as possible of an ACE inhibitor (or ARB), beta-blocker, MRA, and diuretic.	IIa	B	204
Moxonidine is NOT recommended because of safety concerns (increased mortality).	III	B	203
Alpha-adrenoceptor antagonists are NOT recommended because of safety concerns (neurohumoral activation, fluid retention, worsening HF).	III	A	202, 206, 207

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; HF = heart failure; LV = left ventricular; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a]Class of recommendation.

Tabela 5. Preporuke kod izolovane sistolne hipertenzije u srčanoj slabosti

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Abstract

Treatment of arterial hypertension in the light of new guidelines

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We present a patient who was admitted to our hospital with symptoms and signs of hypertension, irregular heart rhytm suggestive of arrhythmia absoluta, and heart failure.

Key words: *heart failure, arterial hypertension, atrial fibrilation*

Srce i krvni sudovi 2014; 33(4):246-248

Prikaz pacijenta

Bolesnik sa valvularnom manom koji se sprema za nekardijalnu hirurgiju

Nataša Janković[1], Dragan V. Simić[1,2], Ognjen Gudelj[3], Dijana Đikić[1], Vladan Kovačević[1], Ivana Petrović[1], Milan Marinković[1], Aleksandar Kocijančić[1], Nebojša Mujović[1,2]

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Sažetak Pacijenti sa valvularnim bolestima su u povećanom riziku od perioperativnih kardiovaskularnih komplikacija tokom nekardijalne hirurgije. Rizik je veoma varijabilan i zavisi od tipa i težine valvularne bolesti, kao i od tipa nekardijalne hirurške intervencije. U slučaju elektivnih nekardijalnih operacija, prisustvo simptoma je presudno za donošenje odluke, a kod asimptomatskih pacijenata nekardijalna operacija malog ili umerenog rizika može se bezbedno izvesti. Prikazan je slučaj bolesnika starog 68 godina koji je imao tesnu aortnu stenozu koja je zahtevala hiruršku intervenciju, zamenu aortne valvule, a sa druge strane imao je i značajnu ingvinalnu herniju koja je takođe zahtevala hirurško rešavanje. Dilema je bila da li pacijenta uputiti prvo na zamenu aortne valvule ili na operaciju ingvinalne hernije. U skladu sa najnovijim preporukama Evropskog udruženja kardiologa za lečenje bolesnika sa valvularnim manama koji se upućuju na nekardijalnu hirurgiju, bolesnik je najpre upućen na kardiohirurgiju gde mu je implantirana veštačka aortna valvula, a nakon potpunog oporavka od kardiohirurške intervencije upućen je na hernioplastiku.

Ključne reči valvularne mane, aortna stenoza, nekardijalna hirugija

Uvod

Širom sveta nekardijalna hirurgija udružena je sa komplikacijama u 7–11 % slučajeva, a stopa smrtnosti iznosi 0,8–1,5 %[1]. Čak do 42 % od ovoga je uzrokovano kardijalnim komplikacijama[2]. Rizik od perioperativnih komplikacija zavisi od opšteg stanja pacijenta pre hirurške intervencije, prisustva komorbiditeta, hitnosti, tipa i trajanja hirurške procedure[3]. Kardijalne komplikacije nakon nekardijalne hirurgije zavise od faktora rizika koji su vezani za samog pacijenta, od tipa hirurške procedure i od okolnosti pod kojima se procedura odvija[4]. Hirurški faktori koji utiču na kardijalni rizik su povezani sa hitnošću, invazivnošću, tipom i trajanjem procedure, kao i sa promenama u telesnoj temperaturi, izmenama u telesnim tečnostima i gubitkom krvi[5].

U odnosu na kardijalni rizik, sve hirurške intervencije, uključujući i otvorene hirurške i endoskopske procedure, mogu se podeliti na one sa malim (<1 %), srednjim (1-5 %) i visokim rizikom (>5 %) – podela izvršena prema 30-dnevnom riziku od kardijalnog događaja (kardijalna smrt i infarkt miokarda) – Tabela 1.

Prikaz pacijenta

Muškarac star 68 godina primljen je na Kliniku za kardiologiju, Kliničkog centra Srbije zbog tegoba u vidu stežućih bolova u grudima, gušenja i omaglica. Nije gubio svest, ali je u više navrata imao kratkotrajne omaglice. Unazad pet godina znao je za šum na srcu. Takođe, pacijent je imao verifikovanu ingvinalnu herniju sa desne strene koja se manifestovala nelagodnošću, bolom i napetošću u preponama, a povremeno je imao i smetnje sa mokrenjem. Pregledan je od strane abdominalnog hirurga koji je indikovao operativno lečenje. Po prijemu na Kardiologiju, pacijent je najpre upućen na ehokardiografski pregled koji je pokazao prisustvo tesne kalcifikovane aortne stenoze sa maksimalnim gradijentom nad aortom od 94 mmHg, srednjim 55 mmHg i površinom aortnog ušća 0,5 cm2; leva komora normalnih dimenzija (EDD 4,8 cm, ESD 2,7 cm), hipertrofična (septum 1,4 cm, zadnji zid 1,4 cm) sa očuvanom ejekcionom frakcijom (EF 67 %). Urađena je selektivna koronarografija kojom nisu nađene angiografski značajne stenoze na koronarnim arterijama. Prema aktuelnim preporukama Evropskog udruženja kardiologa za lečenje valvularnih bolesti srca, zamena aortne valvule je indikovana kod svih pacijenata sa teškom aortnom stenozom i bilo kojim simptomom koji je u vezi sa aortnom stenozom[6]. S obzirom da je naš pacijent imao tesnu aortnu stenozu, zamena aortne valvule je bila apsolutno indikovana. Dilema je bila da li pacijenta uputiti prvo na zamenu aortne valvule ili na operaciju ingvinalne hernije. Najnovije preporuke Evropskog udruženja kardiologa za lečenje bolesnika sa valvularnim manama koji se upućuju na nekardijalnu hirurgiju kažu da se zamena aortne valvule preporučuje kod simptomatskih pacijenata sa teškom aortnom stenozom kod kojih je planirana elektivna ne-

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Tabela 1. Hirurški rizik procenjen prema tipu hirurgije ili intervencije

Mali rizik: < 1 %	Umereni rizik: 1–5 %	Visok rizik: > 5 %
• Površna hirurgija	• Intraperitonealna: splenektomija, hijatus hernija, holecistektomija	• Hirurgija aorte i major vaskularna hirurgija
• Grudi	• Karotidna simptomatska (CEA ili CAS)	• Revaskularizacija donjih ekstremiteta ili trombektomija
• Zubi	• Periferna arterijska angioplastika	• Duodeno-pankreasna hirurgija
• Endokrinološke: tireoidea	• Reparacija endovaskularne aneurizme	• Resekcija jetre, hirurgija žučnih puteva
• Oči	• Hirurgija glave i vrata	• Ezofagektomija
• Rekonstruktivna	• Neurološka i ortopedska: major (hirurgija kuka i kičme)	• Reparacija perforiranih creva
• Karotidna asimptomatska (CEA ili CAS)	• Urološka ili ginekološka: major	• Resekcija nadbubrežnih žlezda
• Ginekološke: minor	• Transplantacija bubrega	• Totalna cistektomija
• Ortopedske: minor (menisektomija)	• Intra-torakalna: non-major	• Pneumonektomija
• Urološke: minor (TUR prostate)		• Transplantacija pluća ili jetre

CAS-carotid artery stenting, CEA-carotid endarterectomy, TUR-transuretralna resekcija prostate

Tabela 2. Preporuke

Preporuke	Klasa	Nivo dokaza
Klinička i ekohardiografska evaluacija se preporučuje kod svih pacijenata sa poznatom ili suspektnom bolešću valvula kod kojih je planirana elektivna nekardijalna operacija umerenog ili visokog rizika.	I	C
Zamena aortne valvule se preporučuje kod simptomatskih pacijenata sa teškom aortnom stenozom kod kojih je planirana elektivna nekardijalna operacija pod uslovom da nisu u visokom riziku od negativnog ishoda valvularne hirurgije.	I	B
Zamenu aortne valvule treba razmotriti kod asimptomatskih pacijenata sa teškom aortnom stenozom kod kojih je planirana elektivna visoko-rizična nekardijalna operacija pod uslovom da nisu u visokom riziku od negativnog ishoda valvularne hirurgije.	IIa	C
Elektivnu nekardijalnu operaciju malog ili srednjeg rizika treba razmotriti kod asimptomatskih pacijenata sa teškom aortnom stenozom ukoliko nije bilo prethodne intervencije na aortoj valvuli.	IIa	C
Simptomatski pacijenati sa teškom aortnom stenozom kod kojih je planirana elektivna nekardijalna operacija, TAVI ili balon valvularna angioplastika treba da budu razmotreni od strane ekspertskog tima ukoliko postoji povećan rizik od negativnog ishoda valvularne hirurgije.	IIa	C

kardiohirurška operacija pod uslovom da nisu u visokom riziku od negativnog ishoda valvularne hirurgije – Tabela 2[3]. U skladu sa tim, pacijent je najpre upućen na kardiohirurgiju gde mu je urađena implantacija veštačke mehaničke aortne valvule St.Jude No 27. Nakon tri meseca i potpunog oporavka od kardiohirurše intervencije, pacijentu je urađena hernioplastika u opštoj anesteziji uz prevenciju infektivnog endokarditisa.

Diskusija

Iako su valvularne bolesti srca ređe nego koronarna bolest, srčana insuficijencija i hipertenzija, one se ipak često javljaju i često zahtevaju neku intervenciju. Najčešća valvularna mana u Evropi i Severnoj Americi je aortna stenoza, naročito među starijom populacijom (2–7 % kod starijih od 65 godina)[7,8].

Pacijenti sa valvularnim bolestima su u povećanom riziku od perioperativnih kardiovaskularnih komplikacija tokom nekardijalne hirurgije[9]. Rizik je veoma varijabilan i zavisi od tipa i težine valvularne bolesti, kao i od tipa nekardijalne hirurške intervencije.

Ehokardiografski pregled bi trebalo uraditi kod svih pacijenata koji idu na nekardijalnu hirurgiju, a imaju poznatu ili suspektnu valvularnu bolest, kako bi se procenila težina valvularne bolesti i eventualne posledice. Ovo se naročito odnosi na pacijente kod kojih se registruje srčani šum. U prisustvu teške valvularne bolesti, preporučuje se klinička i ehokardiografska evaluacija i ukoliko je neophodno da se leči pre nekardijalne hirurgije. Najvažnije je proceniti težinu valvularne bolesti, simptome i njihov odnos sa prisustvom valvularne mane i proceniti rizik od valvularne intervencije i kardijalnih komplikacija u odnosu na tip nekardijalne hirurgije[3].

U slučaju elektivnih nekardijalnih operacija prisustvo simptoma je presudno za donošenje odluke, a kod asimptomatskih pacijenata nekardijalna operacija malog ili umerenog rizika može se bezbedno izvesti[3].

Što se tiče izbora hirurškog pristupa (laparoskopski ili otvoren hirurški pristup), preporučuje se preoperativna procena rizika nezavisno od hirurškog pristupa[3]. U odnosu na otvorene hirurške intervencije, laparoskopske procedure su povezane sa bržim postoperativnim oporavkom, kraćim trajanjem hospitalizacija i manjim brojem komplikacija[10]. Dok zdrave osobe uglavnom dobro tolerišu pneumoperitoneum koji je neophodan za izvođenje laparoskopskih intervencija, kod srčanih bolesnika mogu nastati brojne komplikacije[11]. Pneumoperitoneum i Trendelenburgov položaj povećavaju srednji arterijski pritisak, centralni venski pritisak, srednji pulmonalni pritisak, kapilarni pritisak u plućima i sistemsku vaskularnu rezistenciju, a sve to može da naruši srčanu funkciju[12,13]. Stoga, u

poređenju sa otvorenom hirurgijom, kardiološki rizik kod pacijenata sa srčanom insuficijencijom koji se upućuju na laparoskopsku intervenciju nije manji[14]. Uzimajući sve ovo u obzir u donošenju odluke o tipu hirurške intervencije, presudno je iskustvo i procena hirurga.

Prikazan je bolesnik koji je imao značajnu simptomatsku valvularnu manu –- tesnu kalcifikovanu aortnu stenozu koja je zahtevala hirurško korekciju, tj. zamenu aortne valvule, a sa druge strane, bolesnik je imao i ingvinalnu herniju koja je takođe zahtevala hirurško rešavanje. Imajući u vidu najnovije preporuke Evropskog udruženja kardiologa za lečenje bolesnika sa valvularnim manama koji se upućuju na nekardijalnu hirurgiju, naš pacijent je najpre upućen na Kliniku za kardiohirurgiju gde mu je implantirana veštačka mehanička aortna valvula, a nakon potpunog oporavka upućen je na elektivnu operaciju ingvinalne hernije.

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Abstract

A patient with valvular heart disease getting prepared for non-cardiac surgery: Case Report

Nataša Janković[1], Dragan V. Simić[1,2], Ognjen Gudelj[3], Dijana Đikić[1], Vladan Kovačević[1], Ivana Petrović[1], Milan Marinković[1], Aleksandar Kocijančić[1], Nebojša Mujović[1,2]

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Patients with valvular heart disease are at increased risk of perioperative cardiovascular complications during non-cardiac surgery. The risk is highly variable, according to the type of valvular heart disease and severity of non-cardiac surgery. In the case of elective non-cardiac surgery, the presence of symptoms is crucial for decision. In asymptomatic patients, non-cardiac surgery with small or moderate risk can be performed safely. We presented a case of a 68-year-old patient who had severe aortic stenosis that required surgical treatment, aortic valve replacement, whereas on the other hand he also had a significant inguinal hernia, which also required surgical treatment. The dilemma was what to do first - aortic valve replacement or hernioplasty. According to the new guidelines of the European society of cardiology for the treatment of patients who have valvular heart disease and are sent to non-cardiac surgery, the patient was sent to have aortic valve replacement first, and after complete recovery from cardiac surgery, he was submitted for hernioplasty.

Keywords: *valvular heart disease, aoraortic stenosis, non-cardiac surgery*

Srce i krvni sudovi 2014; 33(4):249-250

Prikaz pacijenta

Hronična srčana insuficijencija – maligna bolest?

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Sažetak Prikazujemo pacijentkinju sa progresijom peripartalne srčane insuficijencije, anuloplastikom mitralnog i trikuspidalnog anulusa i ugrađenim kardioverter-defibrilatorom koja je stavljena na transplant listu srca i bubrega.

Ključne reči peripartalna miokardiopatija, terminalna srčana insuficijencija

Uvod

Oko trećine bolesnika koje srećemo u svakodnevnoj praksi boluje od hronične srčane insuficijencije (SI).

Njihova prognoza nije ohrabrujuća. Očekuje se da oko polovine umre u narednih pet godina od postavljanja dijagnoze. Ciljevi lečenja ovakvih bolesnika su da ih oslobodimo simptoma, da imaju dobar kvalitet života, da se što ređe hospitalizuju i da im produžimo život. Za hroničan tok bolesti terapija je usmerena ka održavanju balansa miokardne potrošnje i funkcionalnog kapaciteta. Hroničnu srčanu insuficijenciju ne možemo izlečiti, ali možemo održavati ravnotežu koja ne dozvoljava akutnu dekompenzaciju. Fokus ranijih kliničkih ispitivanja je bio uglavnom mortalitet, sada se prepoznaje da je sprečavanje hospitalizacija zbog SI važno i za bolesnike i za zdravstveni sistem, kao i popravljanje kvaliteta života ovih bolesnika.[1]

Prikaz pacijenta

Bolesnica, sada starosti 45 godina, kojoj je dijagnoza peripartalne SI postavljena pre 12 godina posle njenog trećeg porođaja. Peripartalna kardiomiopatija je bolest nepoznatog uzroka gde se disfunkcija leve komore javlja tokom zadnjeg tromesečja trudnoće ili u ranom puerperijumu. Učestalost je 1:1300 do 1:4000 majki živorođene dece.[2] Poznato je da se češće javlja kod multipara (kao u slučaju naše pacijentkinje). Bez obzira na optimalnu terapiju, pogoršanje funkcije leve komore (LK) se javlja u preko 50 % slučajeva.[3] Ejekciona frakcija LK<40 % je prediktor visokog rizika. Našoj pacijentkinji je 2002. g. izmerena ejekciona oko 40 % (area-length metodom). Iste godine je urađena koronarografija (kojom je isključena ishemijska etiologija SI) i biopsija miokarda, posle koje je nastavljena medikamentna terapija hronične SI. Terapija hronične SI kod ove pacijentkinje je klasična i nije se značajno menjala tokom ovih 12 godina, menjale su se uglavnom samo doze upotrebljenih lekova. Tri klase neurohumoralnih antagonista: 1. Inhibitori angiotenzin konvertujućeg enzima (ACE I) (ili blokatori angitenzinskih receptora-ARB), 2. beta blokatori, i 3. antagonisti mineralokortikodnih receptora (MRA) – fundamentalno su važni u modifikovanju toka sistolne SI i smanjenju mortaliteta, i trebalo bi ih dati svakom pacijentu što pre posle postavljanja dijagnoze SI (**Klasa IA**).[1] Njima se često dodaju diuretici, za koje nema dokaza da produžavaju život, ali se koriste u cilju smanjenja simptoma i znakova kongestije, tj. postizanja i održavanja euvolemije (pacijentove „suve težine") i to sa najmanjom mogućom dozom. Diuretici petlje su obično prioritetniji od tiazidnih diuretika kod sistolne SI, mada deluju sinergistički i njihova kombinacija može da se koristi (obično privremeno) za lečenje rezistentnih edema.[2]

U narednih 5 godina pacijentkinja je hemodinamski stabilna, uglavnom sa NYHA II klasom, retko NYHA III i to sa terapijom: maksimalna doza betablokera (50 mg karvedilola) uz ACE-I (tbl. monopril 5 mg), MRA (tbl. aldacton 25 mg) i diuretik (furosemid 40 mg/dan).

Godine 2007. se dešava prva rehospitalizacija za ovih 12 godina, kada primećujemo da je mitralna insuficijencija sve veća, kao i sve veći pritisak u desnoj komori (plućnoj cirkulaciji). Tada pojačavamo diuretik (furosemid 2 tablete, tj. 80 mg/dan) i dodajemo amiodaron 1x1 zbog potvrđene kratkotrajne ventrikularne tahikardije (VT). Uprkos pojačanju terapije, bolest napreduje, te 2008. godine nalazimo još veće volumene leve komore (EDV 263 ml) i održanje povišenog sistolnog pritiska u desnoj komori (SPDK) (oko 45 mm Hg).

Zato je juna 2008. godine urađena anuloplastika mitralnog i trikuspidnog prstena i skraćenje hordi za A2 segment prednjeg mitralnog kuspisa. Kontrolni eho srca ubrzo posle operacije pokazuje smanjene dimenzija leve pretkomore i LK, smanjene volumene (smanjenje EDV LK za oko 100 ml) i normalni pritisak u desnom srcu. Zbog toga je i smanjena doza diuretika (furosemid na 40 mg/III dan). Nažalost, ubrzo posle operacije postavljena je sumnja na rupturu tercijalne horde, zbog koje mitralna insuficijencija postepeno opet progredira sa svim svojim posledicama, te je bilo potrebno pojačanje terapije, pre svega doze diuretika (furosemid 40mg/dan). Bitan cilj kod bolesnika sa hroničnom SI je da se izbegne kongestija, jer je ona glavni razlog rehospitalizacija, a sa brojem rehospitalizacija raste i smrtnost. Sa daljim napredovanjem bolesti i porastom sistolnog pritiska u de-

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snom srcu (do 72 mmHg), prinuđeni smo da opet povećavamo dozu diuretika 40–80mg/dan, uz „žrtvovanje" ACE I (na račun ukidanja ACE I) zbog održavanja tenzije. A 2009. godine urađena je i ugradnja veštačke mitralne valvule.

Godine 2010. ugrađen joj je i kardioverter-defibrilator (ICD) u primarnoj prevenciji naprasne srčane smrti (IA klasa preporuka). Zbog QRS kompeksa kraćeg trajanja od 120 ms nije bilo indikacija za ugradnju CRT. Oko polovine smrti kod pacijenata sa SI, posebno kod onih sa blažim simptomima, dešava se iznenada i neočekivano i mnoge, ako ne i većina, od njih su zbog ventrikularnih aritmija. Prevencija naprasne smrti je stoga značajan cilj kod SI. Do sada je kod ove pacijentkinje bio efikasan-uključivan samo jednom 2012. godine (kad je brza VT prešla u VF).

Od 2010. godine do danas kod bolesnice se, uprkos optimalnoj terapiji, dešava progresija srčane slabosti (EF sa nekih 18 % se svela na 9 % koliko se održava zadnjih godinu dana). Od komorbiditeta došlo je do porasta serumskih vrednosti kreatinina i održavaju se vrednosti - 115-131 µmol/L, što znači da dolazi do slabljena bubrežne funkcije. Stopa glomerulske filtracije (GFR) je smanjena kod većine pacijenata sa SI, posebno u odmaklim stadijumima i renalna funkcija je moćan nezavisan prediktor prognoze u SI.[1] Blokatori sistema renin-angiotenzin-aldosteron blokatori (ACE inhibitori, inhibitori renina, ARB I MRA) često uzrokuju pad GFR, mada je redukcija obično mala. Osim hipotenzije koja je dobro poznati uzrok renalne disfunkcije, manje je poznato da opterećenje volumenom, insuficijencija desne komore i renalna venska kongestija mogu takođe da uzrokuju renalnu disfunkciju.[1] Takođe se kod pacijenata sa bubrežnim pogoršanjem javlja i manji odgovor na diuretike. Rezistencija na diuretike se neminovno javlja tokom hronične upotrebe diuretika i prediktor je lošeg ishoda. Može se pokušati sa prevazilaženjem ovog problema kombinovanjem više diuretika koji deluju na različitim nivoima nefrona, ali uglavnom privremeno, što je kod naše pacijentkinje pokušavano u toku poslednjih hospitalizacija, ali je obično bilo praćeno i pogoršanjem bubrežne funkcije, što je onemogućavalo ovakav terapijski pristup.

Tokom 2014. godine sa EF oko 8 % i jako malim Clir od 1.8 ml/min./m^2, stavljena na program za transplantaciju srca i bubrega (zadnja procenjena GFR oko 35 ml/min.).

Diskusija

Gde je naša pacijentkinja danas? Još uvek kod kuće, funkcioniše sa sistolnim KP od max 90 mmHg. Od terapije koristi: minimalnu dozu betablokatora (tbl. bisoprolol 1.25 mg) i maksimalnu dozu diuretika (500 mg edemida) (po vodičima preporučena uobičajena dnevna doza 40–240 mg i sa maksimalnom ukupnom dnevnom dozom od 600 mg[1,2]), u kombinaciji sa diuretikom petlje (aldactone 25 mg) uz oralnu antikoagulantnu terapiju, amiodaron ½, trimetazidin 2x35 mg. Poslednja dva meseca je u NYHA IV stadijumu i sa sve većom kardijalnom kaheksijom.

Pacijenti sa terminalnim stadijumom srčane slabosti imaju slab kvalitet života i veoma visoku stopu mortaliteta.[4] Mada je transplantacija srca udružena sa visokom stopom preživljavanja – od jedne do deset godina, ograničen je broj donora, tako da ovi bolesnici postaju potencijalni kandidati za implantiranje nekog od novih mehaničkih uređaja. Termin mehanička cirkulatorna potpora (MCS) opisuje različite tehnologije koje se koriste da obezbede kratkotrajnu i dugotrajnu pomoć kod pacijenata sa srčanom insuficijencijom. Najveće iskustvo sa MCS je u terminalnom stadijumu, inicijalno kao premošćavanje do transplantacije srca (BTT), ali u poslednje vreme sve više se koristi kao konačna terapija (*destination terapy*), kod pacijenata koji nisu pogodni za transplantaciju srca.[1]

Za ugradnju ovih uređaja je ključna procena funkcije desne komore, jer postoperativna slabost desne komore jako povećava postoperativni mortalitet i smanjuje preživljavanje kako pre, tako i posle transplantacije. Stoga bi za premošćavanje do transplantacije trebalo razmotriti biventrikularne uređaje (BiVAD) pre nego LVAD potporu kod pacijenata sa globalnom srčanom insuficijencijom (kao što je slučaj kod naše pacijentkinje sa značajnom slabošću desne komore).

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Abstract

Chronic heart failure – a malignant disease?

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We pesent a patient with progression of peripartal heart failure, anuloplasty of mitral and tricuspid anulus, implantation of cardioverter defibiltaor and who is now a candidate for heart/renal transplant.

Key words: *peripartal cardiomyopathy, end-stage heart failure*

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Prikaz pacijenta

Prikaz slučaja bolesnice sa hipertrofičnom neopstruktivnom kardiomiopatijom u svetlu Evropskih preporuka za dijagnozu i lečenje hipertrofične kardiomiopatije

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Sažetak Hipertrofična kardiomiopatija je bolest sa značajnom prevalencom u opštoj populaciji (1~500). Klinički tok može biti raznovrstan. Najveći broj bolesnika doživi duboku starost bez tegoba. Manji deo je u riziku za naglu srčanu smrt i poremećaje ritma, a najmanji progredira u srčanu slabost. Prikazujemo slučaj bolesnice koja je praćena klinički i ehokardiografski na našoj klinici od svoje 10 godine kada joj je dijagnostikovana hipertrofična kardiomiopatija do 44 godine starosti kada se javljaju simptomi i znaci srčanog popuštanja.

Ključne reči hipertrofična miokardiopatija, srčana insuficijencija

Uvod

Kardiomiopatija je bolest miokarda u kojoj je miokard strukturno i funkcionalno patološki izmenjen u odsustvu koronarne bolesti, hipertenzije, valvularnih mana ili kongenitalnih anomalija. Hipertrofična kardiomiopatija (HCM) je najčešća kardiomiopatija (prevalenca 1:500). Kod bolesnika postoji značajna raznovrsnost po pitanju kliničkog toka, starosti u trenutku javljanja bolesti, prisustva i odsustva simptoma, stepena zadebljanja mišića, stepena opstrukcija u izlaznom traktu, rizika od iznenadne srčane smrti.[2] Većina bolesnika ima stabilan, benigni klinički tok. Ostali mogu da dožive naglu srčanu smrt, poremećaje srčanog ritma (najčešće atrijalna fibrilacija) i u malom procentu (5–10 %) progresiju u simptomatsku srčanu slabost.[1,2]

Prikaz bolesnika

Bolesnica stara 44 godine javlja se na kontrolni pregled zbog zamaranja. Na pregledu je utvrđeno da je kardiopulmonalno kompenzovana. Srčana akcija ritmična, tonovi jasni sa blagim sistolnim šumom nad vrhom srca. Nalaz nad plućima uredan. Arterijski pritisak 110/70 mmHg. Trenutna terapija sadrži beta blokator, ACE inhibitor i diuretik.

Praćenje se sprovodi u KCS od 1986. godine. Prve tegobe su se javile sa 10 godina starosti u vidu zamaranja i gušenja kada je otkriven sistolni šum nad prekordijumom i postavljena sumnja za ventrikularni septalni defekt, da bi 5 godina kasnije ehokardiografskim pregledom bilo ptvrđeno postojanje hipertrofične kardiomiopatije (HCM). Elektrokardiografski (EKG) snimak je opisan kao sugestivan za postojanje WPW sindroma.

Endomiokardna biopsija je urađena kada je bolesnica imala 20 godina, a nalaz je pokazao veoma umnoženo vezivo, sa elastičnim i kolagenim vlaknima između mišićnih vlakana. Jedra miofibrila bila su veća i hiperhromatična i nije bilo znakova zapaljenske infiltracije.

Rutinski je rađen **24 Holter EKG** svake dve godine, i nisu zabeleženi poremećaji ritma do njene 36. godine života kada je registrovana paroksizmalna atrijalna fibrilacija koja je trajala tri dana. Tri godine kasnije prvi put se Holterom beleži kratkotrajna ventrikularna tahikardija frekvence 160/min.

Ehokardiografsko praćenje je pokazalo progresivno uvećanje šupljine leve komore sa smanjenjem debljine zidova i uvećanje leve pretkomore (Tabela 1, slike 1, 2, 3).

Bolesnica je imala tri trudnoće (sa 33, 35 i 38 godina starosti) koje su protekle bez komplikacija i završene su carskim rezom u opštoj anesteziji. Kod šestogodišnje ćerke ehokardiografski je registrovano zadebljanje zidova LK, a kod rođene sestre je potvrđena HCM. Genetsko ispitivanje je u toku.

Diskusija

Bolest je uglavnom asimptomatska i otkriva se slučajno tokom rutinskog sistematskog pregleda. Bolesnik se upućuje na ehokardiografski pregled zbog promena u EKG-u ili prisustva šuma na srcu. Najčešći simptom je dispnea. Dijagnoza se postavlja ehokardiografski nala-

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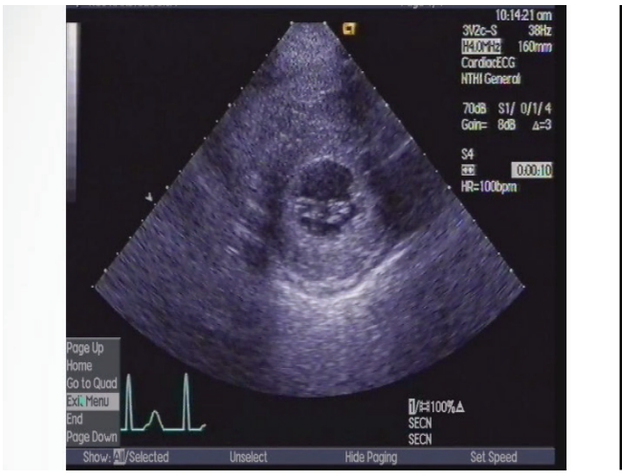
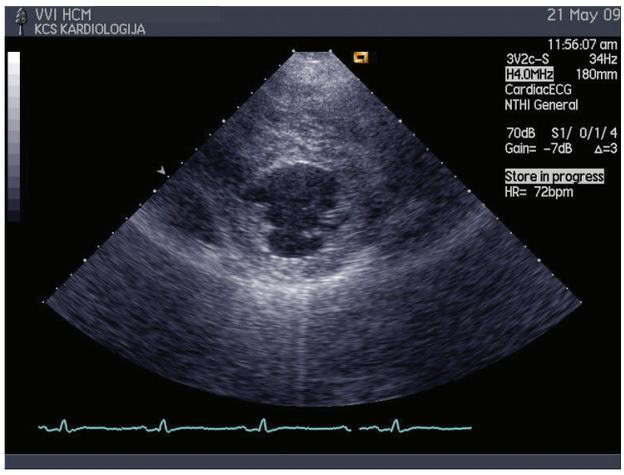
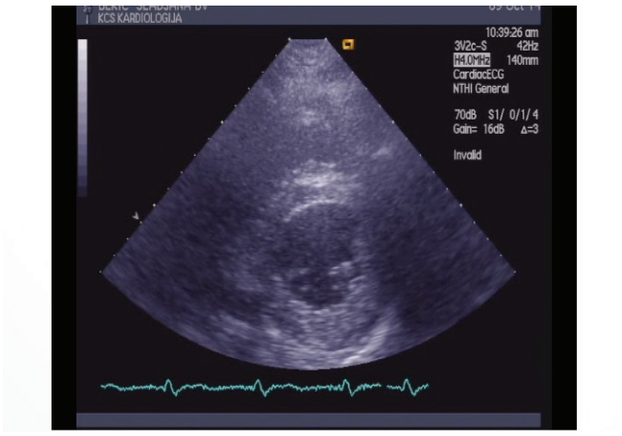


Slika 1. Hipertrofična miokardiopatija (ehokardiografski presek 2007. godine)



Slika 2. Hipertrofična miokardiopatija (ehokardiografski presek 2009. godine)



Slika 3. Hipertrofična miokardiopatija (ehokardiografski presek 2014. godine)

Tabela 1. Promene ehokardiografskih parametara tokom perioda praćenja

Godina pregleda	EDD LK (cm)	ESD LK (cm)	IVS d (cm)	ZZd (cm)	EF LK (%)	LA (cm)
1985.			2.5			
1997.	4.1	2.1	2.7	1.4	80	3.1
1999.	3.9	1.9	3.1	1.4		3.9
2002.	4.4	2.1	2.7	1.3	80	3.8
2006.	4.9	3.4	2.3	1.2	65	3.8
2009.	5.1	3.5	1.8	1.1	58	3.1
2013.	5.8	4.1	1.6	0.9	54	4.3
2014.	5.9	4.5	1.2	0.9	46	4.6

LK – leva komora; EDD LK – end-dijastolna dimenzija LK; ESD LK – end-sistolna dimenzija LK; IVSd – debljina septuma u dijastoli; ZZd – debljina zadnjeg zida LK u dijastoli; EF LK – ejekciona frakcija LK; LA – veličina leve pretkomore

zom nedilatirane leve komore, debljine zidova ≥15 mm kod probanda ili ≥13 mm kod rođaka bolesnika sa HCM). Hipertrofija je najčešće asimetrična sa dominantnim zadebljanjem interventrikularnog septuma, ali može biti i koncentrična ili apikalna (kada su zahvaćeni samo apikalni segmenti zidova LK). Patohistološki supstrat predstavljaju nepravilno raspoređene srčane hipertrofične ćelije, bizarnog oblika, sa multiplim međućelijskim vezama u svim pravcima i sa poljima fibroze. Ta ćelijska dezorganizovanost može biti veoma rasprostranjena zahvatajući i do 33 % zida. Intramuralne koronarne arterije su takođe izmenjene, zadebljalog zida i suženog lumena. Kod oko 25 % bolesnika dolazi do opstrukcije u levoj komori u toku sistole, najčešće u izlaznom traktu, ali može biti na bilo kom nivou u komori. Opstrukcija je dinamska, a gradijent preko 60 mmHg se smatra klinički značajnim.

Genetička ispitivanja

HCM je kod 40–60 % bolesnika nasledna bolest kontraktilnih proteina sarkomera koja pokazuje veliku genetsku heterogenost i uglavnom se nasleđuje autotozomno dominantno. Identifikovano je preko 15 gena i 400 mutacija tako da ekspresija značajno varira i kod nosilaca iste genetske mutacije.[3] U 10–15 % slučajeva zadebljanja srčanog mišića su posledica bolesti deponovanja (glikogenoza, amiloidoza), a javlja se i u sklopu retkih malformacionih sindroma (Noonanov sindrom, LEOPARD sindrom), kao i mitohondrijalnih i neuromišićnih bolesti (Fridrajhova ataksija). Genetičo ispitivanje je preporučeno kod bliskih rođaka bolesnika sa jasno definisanom mutacijom (kod dece nakon navršene 10 godine života).

Kliničko paćenje i lečenje

Praćenje bolesnika je pre svega elektrokardiografsko i ehokardiografsko na 1–2 godine između 10 i 20 godine života, a nakon toga na 2–5 godina.[4]

Terapija je simptomatska i preventivna. Otežano disanje i bol u grudima su najčešći simptomi. Javljaju se zbog dijastolne disfunkcije, poremećene mikrocirkulacije i opstruktivnih patofizioloških poremećaja. Beta blokatori su lekovi izbora. Kod bolesnika sa dinamskim gradijentom u izlaznom traktu treba izbegavati vazodilatatore i diuretike i razmotriti mogućnost redukcije debljine interventrikularnog septuma (hirurški ili alkoholnom ablacijom). Atrijalna fibrilacija i srčana insuficijencija se leče prema važećim preporukama.

Bolesnici sa HCM su u povećanom riziku za iznenadnu srčanu smrt.[5] Faktori rizika su: godine starosti (veća incidence kod mlađih bolesnika), srčani zastoj (komorska fibrilacija), spontana komorska tahikardija (sustained i nonsustained), istorija iznenadne srčane smrti u porodici, debljina zida leve komore preko 30mm, nenormalan odgovor krvnog pritiska (pad) pri opterećenju, opstrukcija izlaznog trakta leve komore.

Kod bolesnika sa dva ili više faktora rizika za iznenadnu srčanu smrt indikovano je postavljanje implantibilnog kardioverter defibrilatora (ICD).[5] Ukoliko se ne implantira ICD indikovana je periodična procena faktora rizika, svakih 12–24 meseci.

Kod bolesnika kod kojih se razvije dilatacija komore i srčano popuštanje indikovana je transplantacija srca.

S obzirom da je bolest uglavnom benignog toka uloga lekara je pre svega u pružanju psihološke potpore obolelom i njegovoj porodici. Zdrav životni stil koji podrazumeva i rekreativno bavljenje sportom je preporučljiv. Nije dozvoljeno bavljenje kompetitivnim sportovima.

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Abstract

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Hypertrophic cardiomyoparthy is disease with very high prevalence in general population (1~500). There is marcable diversity in disease course. Majority of patients have benign clinical course and normal life expactancy but some are in risc for sudden cardiac death, severe arrhythmia and progressive heart failure. We present a case of female patient who was diagnosed with hypertrophic cardiomyopathy as a child (10years). She was clinicaly and echocardiographicly followed up in our clinic. When she was 44 years old signs and symptoms of heart failure started to develop.

Key words: *hypertrophic cardiomyopathy, heart failure*

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Abstract Unstable coronary artery plaque is the most common underlying cause of acute coronary syndromes (ACS) and can manifest as unstable angina, non-ST segment elevation infarction (NSTE-ACS), and ST elevation myocardial infarction (STEMI), but can also manifest as sudden cardiac arrest due to ischaemia induced tachyarrhythmias. ACS mortality has decreased significantly over the last few years, especially from the more extreme manifestations of ACS, STEMI, and cardiac arrest. This trend is likely to continue based on recent therapeutic progress which includes novel antiplatelet agents such as prasugrel, ticagrelor, and cangrelor.

Introduction

In the USA every year nearly 1.2 million patients are hospitalised for acute coronary syndrome (ACS).[1] However, the proportion of ACS with ST elevation myocardial infarction (STEMI) appears to be declining.[2 3] We can only speculate upon the reasons: potential explanations include the reduction in smoking, the age structure of the population (STEMI is more common in middle age while non-ST segment elevation (NSTE-ACS) occurs more in the elderly), and broader use of statin therapy. Over the last few years there has been a significant improvement in outcomes after STEMI in regard to mortality, cardiogenic shock, and heart failure.[1] Similar trends have been seen for other manifestations of ACS, such as sudden cardiac arrest (SCA).[4 5] Astonishingly, the clinical outcomes for NSTE-ACS now appear to be worse than for STEMI. However, such figures are misleading, and short term (in-hospital) outcome is still better for NSTE-ACS than for STEMI, while the longer term mortality rate is higher for NSTE-ACS, but this is probably influenced by the different age and risk structure of the STEMI and NSTE-ACS populations: NSTE-ACS patients are generally older and often have multivessel (MV) coronary artery disease (CAD).

ST Elevation Myocardial Infarction

A major reason for the improved outcomes for STEMI over the last decades has been the increasing availability of primary percutaneous coronary intervention (PCI) services, which all try to continuously improve their performance ('door-toballoon time'). Initiatives include telemetric transmission of ECGs from the ambulance services, and training of ambulance staff in ECG interpretation. More important than door-to-balloon time is of course the overall 'symptom onset to balloon time'. Patients have become much better informed about symptoms of 'heart attacks', and many ambulance services transfer patients with a suspected STEMI directly to a primary PCI service rather than going to the nearest hospital.

Primary Percutaneous Coronary Intervention

Not only has the rate of primary PCI increased over the years, but progress in device technologies and adjunctive pharmacology has also improved the procedural success rate—for example, the availability of stents and second generation drug eluting stents, thrombus aspiration devices, and safer and more effective periprocedural anticoagulation/antiplatelet treatments. Thrombus aspiration has been shown to improve outcomes in smaller randomised trials and is currently recommended by European and American PCI guidelines. However, its effect should probably not be overrated. A recent large scale randomised trial in 452 patients, INFUSE-AMI (Intracoronary Abciximab and Aspiration Thrombectomy in Patients with Large Anterior Myocardial Infarction) did not demonstrate an effect of manual thrombus aspiration on infarct size when used in conjunction with bivalirudin (and intracoronary abciximab).[6 7] Intravenous glycoprotein (Gp) IIb/IIIa inhibitors have an immediate and potent platelet inhibitory effect and certainly improve thrombus resolution; they may reduce infarct size[6]

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Table 1. Bleeding avoidance strategies[9]

Strategy	Comments
Radial instead of femoral access	Reduces access site bleeding risk (and potentially also mortality in high risk groups)
Bivalirudin	Bivalirudin superior to heparin and glycoprotein IIb/IIIa inhibitors, reduces bleeding (and reduces mortality in STEMI patients)
Fluoroscopy guided puncture for femoral access	High (or low) puncture to be avoided. The femoral head has a consistent relationship with the common femoral artery, and localisation using fluoroscopy is a useful landmark. However, randomised studies failed to show a clinical benefit but were underpowered
Ultrasound guided puncture for femoral access	Fewer vascular complications with this approach in randomised trials
Vascular closure devices	Controversial study results. Increasing evidence pointing towards a positive effect of vascular closure devices, especially if used with bivalirudin
Individualised bleeding risk assessment	Individualised risk assessment and adjustment of clinical practice using risk models, for example, NCDR CathPCI bleeding risk model (bivalirudin, radial access, etc)

NCDR, National Cardiovascular Database Registry; PCI, percutaneous coronary interventions; STEMI, ST elevation myocardial infarction.

while their effect on clinical outcomes is somewhat more debatable. Bivalirudin, a direct thrombin inhibitor, which has anticoagulant and probably also antiplatelet effects (via suppression of thrombin dependent platelet activation[8]), can be used as an alternative to heparin and Gp IIb/IIIa inhibitors, and has shown reduced bleeding and even reduced mortality in the HORIZON-AMI trial (Heparin plus a glycoprotein IIb/IIIa Inhibitor versus Bivalirudin Monotherapy and Paclitaxel-Eluting Stents versus Bare-Metal Stents in Acute Myocardial Infarction).[6] Bleeding reduction has become a key aim in primary PCI because of the well documented (but less well understood) association with increased mortality (table 1).

Transradial versus transfemoral access

Another rather elegant option used increasingly, which may reduce bleeding, involves the transradial approach instead of the traditional transfemoral access.[9] An increasing wealth of data indicate that this reduces bleeding in general; some data even suggest that it reduces mortality when used for primary PCI, but the latter effect is debatable.[10 11] A recent meta-analysis of nine studies involving 2977 patients with STEMI demonstrated an impressive nearly 50% reduction in mortality for the transradial approach (OR 0.53, 95% CI 0.33 to 0.84; p=0.008).[10] While the authors concluded that the transradial approach should be preferred in STEMI patients, an accompanying editorial highlighted some limitations of these data.[11] Some data indicate a negative impact of transradial PCI. Baklanov et al[12] showed a longer median door-to-balloon time with transradial PCI. Another retrospective comparison by Cafri et al,[13] however, showed similar door-to-balloon time irrespective of the access route. Even in elderly people, where there is more advanced atherosclerosis, the radial access does not seem to delay reperfusion as it does not lead to any increase in the door-to-balloon time.[14] There have also been concerns that transradial access may increase the risk of neurological complications compared to transfemoral access. However, in a retrospective analysis of the British Cardiovascular Intervention Society database conducted between January 2006 and December 2010, Ratib et al[15] have shown that there is no significant association between the use of radial access and the occurrence of neurological complications.

Overall, transradial PCI is certainly a promising technique when used by experienced operators. However, despite its benefits, its use is highly variable across countries. In France and Japan it is the predominant access route.[11] In the UK, its use increased nearly fourfold from 17.2% in 2006 to 57% in 2011.[16] The USA has the lowest rate of radial access adoption for PCI worldwide (only one in six PCIs).[17] Even here, there has been an increase in use of radial access. In the first quarter of 2007, 1.2% of PCIs were by the transradial approach; this increased to 16.1% in the third quarter of 2012. There is little doubt that the increasing use of transradial PCI has led to a reduction in access site complications.[12 16 17 18]

While some data indicate that the transradial route may reduce mortality in STEMI patients, this has not been demonstrated in NSTE-ACS. In the RIVAL (Radial vs Femoral Access for Coronary Intervention) trial, currently the largest randomised trial on this topic, there was no difference in major clinical outcomes in NSTE-ACS patients.[19] In a cohort of high risk NSTE-ACS patients enrolled in the EARLY-ACS trial (Early Glycoprotein IIb/IIIa Inhibition in non-ST-Segment Elevation Acute Coronary Syndrome), there were no significant differences in either bleeding or ischaemic outcomes whether radial or femoral access was used.[20]

A recent consensus statement by the European Society of Cardiology (ESC) states that a default radial approach is feasible in routine practice in both stable and unstable patients.[21] The ESC recommends performing transradial PCI in STEMI patients only after the operator has become familiar with this approach in stable patients and in diagnostic procedures.

Culprit lesion PCI

Culprit lesion only treatment versus a 'complete revascularisation' approach remains the subject of some debate. One could argue either way: a complete revascularisation strategy may improve overall myocardial

perfusion in the critical initial phase; but on the other hand, we know that major adverse complications are increased during acute PCI, and this also may have an impact on the outcome following treatment of non-acute, nonculprit lesions. A randomised study of 214 patients showed that angioplasty of the culprit vessel only was associated with higher rates of adverse events (50.0%) during a mean follow up of
2.5 years than MV PCI, regardless of simultaneous complete revascularisation (23.1%) or a staged complete revascularisation (20.0%).[22] A recent report of the Ibaraki Cardiovascular Assessment Study registry of Japan showed significantly higher mortality with PCI of a non-culprit lesion in the same setting as the culprit lesion than with PCI of only the culprit lesion.[23] In contrast, results based of the American College of Cardiology National Cardiovascular Database Registry (NCDR-CathPCI) showed similar morbidity and mortality rates with either single vessel or MV PCI.[24] While these data were conflicting, most studies were non-randomised and need to be interpreted with caution. A large meta-analysis of 18 randomised controlled trials (RCTs), including the above mentioned RCT, involved 40 280 patients and showed that staged PCI was associated with lower short and long term mortality compared to culprit vessel PCI and MV PCI.[25] Therefore, current guidelines discourage the performance of multivessel PCI for STEMI and suggest that nonculprit lesions should be staged.[26 27] However, if STEMI patients present in cardiogenic shock or after an SCA, they should be considered for complete revascularisation in one sitting.

The time effect

The current ESC guidelines recommend that STEMI patients should be immediately transported within 2 h of onset of symptoms to a PCI-capable centre without delay.[28] In clinical practice, it is extremely difficult to achieve this goal of symptom onset-to-balloon time.[29] System delays have been shown to be associated with mortality at a median follow-up of 3.4 years in STEMI patients treated with primary PCI.[30] In a more recent study, shorter symptom onset-to-balloon time predicted lower mortality in the long term.[31] A longer treatment delay was seen in females, patients living in a rural area >22 km from hospital, and when patients were admitted to the emergency department of the hospital instead of direct emergency medical services (EMS) transportation. Researchers suggest that a more generalised use of ambulance/EMS would reduce treatment delays and associated mortality.

Optimal duration of monitoring/ hospital stay

The duration of hospital stay has decreased dramatically over the years, which has a major impact on health care expenditure and on patient quality of life. Current practice is widely variable across countries and centres, but it is unclear whether early hospital discharges are safe.[32] It is very reassuring that, despite the continuous reduction in hospital stay, outcomes have significantly improved (figure 1).

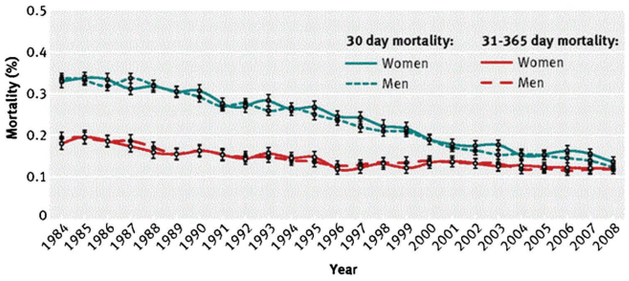

Figure 1. Change in short and intermediate term mortality after ST elevation myocardial infarction. Standardised 30 day and 31–365 day mortality after first hospitalisation for myocardial infarction among men and women between 1984 and 2008 in Denmark.[33] Reprinted with permission from BMJ Publishing Group.

Two new studies have demonstrated that discharging low risk STEMI patients within 2 days following primary PCI is safe and feasible.[34 35] Over 40% of the STEMI patients in one of the studies met early discharge criteria.[34] An early discharge could lower healthcare costs considerably.
Based on the literature, we propose the following criteria to define low risk patients for early discharge:

1. Age <70 years
2. Short pain to reperfusion interval (<4 h)
3. Uncomplicated primary PCI with good result (TIMI (Thrombolysis in Myocardial Infarction) 3 flow and prompt complete ST elevation resolution)
4. Left ventricular ejection fraction >45% without symptoms of heart failure
5. No significant arrhythmias during the first 24 h
6. Socially supported, collaborative/compliant patient.

Non-ST Elevation ACS

Risk prediction

There is a great need for proper risk prediction in ACS patients for clinical decision making, especially with regard to coronary angiography. There are several risk prediction models in use. The Global Registry of Acute Coronary Events (GRACE) is among the most commonly used scores. Recently, a mini-GRACE (MG) risk score has been developed which excludes creatinine and Killip class from the original eight-factor GRACE risk model. The adjusted mini-GRACE (AMG) risk score includes 'prescription of a loop diuretic during admission' in place of Killip class and creatinine concentration. Both risk scores showed good accuracy in the Myocardial Ischaemia National Audit Project (MINAP), with the AMG risk score performing somewhat better than the MG risk score.[36]
Laboratory markers may further help with this risk stratification. The maximal troponin value in patients presenting with NSTE-ACS has been shown to be an independent predictor of in-hospital morbidity and mortality.[37] Other predictive markers include interleukin 10, myeloperoxidase, and placental growth factor.[38]

Role and timing of PCI in NSTE-ACS

For intermediate to high risk patients, there is strong evidence supporting routine angiography rather than conservative management. However, the optimal time for coronary angiography is not clear. Though an early invasive approach seems favourable, studies testing the timing effect used varying time points for 'early' and 'delayed' angiography. In very high risk patients such as those with refractory angina, severe heart failure, life threatening ventricular arrhythmias or haemodynamic instability or an evolving myocardial infarction (MI), an urgent invasive approach is indicated. For patients not belonging to this high risk category, the optimal timing is not clear. There is no clear benefit with regard to 'hard' clinical end points for an early invasive strategy within 24 h, but an increasing number of centres undertake an early invasive strategy within 24 h for intermediate to high risk patients. Such an approach is probably reasonable, as an earlier approach certainly helps to reduce hospital stay. Factors such as diabetes, renal function, left ventricular function, recurrent symptoms, and previous revascularisation should be considered along with the TIMI or GRACE score.

Intravascular imaging

Intravascular imaging guided PCI is a concept that evolved when devices such as intravascular ultrasound (IVUS) and more recently optical coherence tomography (OCT) became available. There are two different modes of use, either for the pre-PCI assessment in order to better understand the coronary plaque (stable or unstable plaque, diameter and length, thrombus burden, etc), or for post-PCI assessment of stent expansion and apposition. The advantages are obvious; in contrast to angiography as an eyeballing tool, which allows measurement of luminal diameters in a few orthogonal views, coronary IVUS provides a tomographic view. Furthermore, the resolution is much better than for angiography.

The first concept, pre-PCI assessment of lesions has been tested in the multicentre PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study.[39] This study showed that IVUS can be used to define characteristics of vulnerable plaques. The highest risk phenotypes associated with non-culprit major adverse cardiac events (MACE) included thin-cap fibroatheromas, plaque burden >70%, and minimal lumen area <4.0 mm. However, these data are not sufficient to advocate using IVUS derived plaque characteristics to decide whether a lesion needs to be treated.[40]

While IVUS is based on ultrasound, OCT is based on light, which has a much shorter wavelength, and therefore achieves 10-fold better spatial resolution compared to IVUS.[41] This allows better definition of the thin fibrous caps and the circumferential extent of the necrotic cores. It helps detect other microstructural features such as cholesterol crystals, thrombus, calcium deposits, fibrous plaques, and lipid-rich plaques.[42] OCT can visualise features not seen by IVUS such as intimal flaps and defects in the intima, disruptions in the media, and stent strut apposition.

A Japanese study that analysed the culprit lesion in AMI patients found that the incidence of plaque rupture observed by OCT was significantly higher than that observed by both angioscopy and IVUS.[43] OCT was also superior in detecting fibrous cap erosion and thin cap fibroatheroma, and OCT could also estimate the fibrous cap thickness.

However, the depth of imaging penetration is limited to only a few millimetres with this new technique.[44] So, it is unable to image the adventitia and assess the plaque burden. Therefore, Alfonso et al[45] had the idea of a combined use of OCT and IVUS in patients with stent thrombosis. Since image length was shorter with OCT, they suggested overlapping OCT runs to circumvent the problem. The challenge of OCT is that it requires a field clear of blood for imaging.

Because OCT has superior resolution to IVUS, it clearly recognises stent struts on heavily calcified areas which are difficult to identify with IVUS. Post-intervention OCT also produces a sharper image of the neointimal–thrombus boundary and provides a reliable diagnosis of in-stent restenosis or neoatherosclerosis. In current practice, OCT and IVUS seem to complement each other with their respective advantages and disadvantages. However, we have to be aware that data on clinical outcomes are limited and that these techniques add to procedural costs.

Antiplatelet therapy

Aspirin is still the basis of every antiplatelet therapy. However, dual antiplatelet therapy of aspirin and a P2Y12 receptor blocker is clearly more effective and clopidogrel is the most commonly used agent for this purpose at the moment. However, the problems with this treatment are the rather long delay until maximal platelet inhibition is reached and the high rate of poor responders.[46] One approach that has been tested repeatedly is triple antiplatelet therapy using cilostazol. Even though results of this approach have indicated some benefit, it is rarely used.[47 48] One reason for this is probably the development of newer generation P2Y12 receptor blockers such as prasugrel, ticagrelor, and cangrelor. They block the binding of ADP to the platelet receptor P2Y12, thereby inhibiting platelet aggregation.

Naturally, we would expect that stronger antiplatelet inhibition comes with an increased bleeding risk. Many patients therefore receive proton pump inhibitors (PPI). However, the data do not completely following this logic.

Prasugrel: The TRITON-TIMI 38 trial was a head-to-head comparison between aspirin and prasugrel versus aspirin plus clopidogrel in 13 608 moderate to high risk ACS patients undergoing PCI. In most cases, the study drug was given after coronary angiography. At 15 months follow-up, MACE (cardiovascular death, non-fatal MI, or non-fatal stroke) was reduced with prasugrel (9.9% vs 12.1%; HR 0.81, 95% CI

0.73 to 0.90) This composite end point was mainly driven by a reduction in non-fatal MI. Major bleeding was somewhat increased with prasugrel (2.4% vs 1.8%; HR 1.32, 95% CI 1.3 to 1.68). Bleeding was mainly increased in those with a history of stroke or transient ischaemic attack, age ≥75 years or a bodyweight ≤60 kg. The TRILOGY ACS trial tested prasugrel versus clopidogrel

with NSTE-ACS not undergoing PCI. There was no statistically significant difference in MACE rate (13.9% vs 16.0%; HR 0.91, 95% CI 0.79 to 1.05).

Ticagrelor: In contrast to clopidogrel and prasugrel, ticagrelor binds reversibly to the P2Y12 platelet receptor. This agent was tested in the PLATO trial (18 624 patients) in patients with ACS, and also those who did not undergo PCI but had medical therapy. Treatment was started early, at a median of 5 h after hospital admission. This study showed a reduced risk for MACE (defined as cardiovascular death, MI, or stroke) in the ticagrelor arm (9.8% vs 11.7%, HR 0.84, 95% CI 0.77 to 0.92), and there was also a reduced risk for cardiovascular mortality as a single end point. Overall, there was no significant difference in the rates of major bleeding between the ticagrelor and clopidogrel groups (11.6% vs 11.2%, respectively). However, there was a higher risk of non-coronary artery bypass surgery related major bleeding (4.5% vs 3.8%).

Cangrelor: In contrast to these drugs, cangrelor is administered intravenously. It has been tested against placebo and against clopidogrel. The CHAMPION-PLATFORM trial (placebo control) was stopped early because an interim analysis showed disappointing results. The CHAMPION-PCI trial (clopidogrel as a comparator) failed to show a significant benefit as well. The most recent and largest study, the CHAMPION-PHOENIX trial, compared cangrelor against preloading with 300–600 mg of clopidogrel. This study not only included ACS but also patients with stable CAD. It found a reduced risk for ischaemic events (death, MI, ischaemia-driven revascularisation or stent thrombosis) over the first 48 h without any increase in major bleeding risk.[49] Its role in clinical practice in the context of having ticagrelor and prasugrel available is not clear yet, and it has never been compared against these agents.

With additional and more potent antiplatelet therapies now available, the challenge is to decide which agent to use and when. Currently, the decision is usually based on clinical and risk factors; pharmacogenetics may also play a role in guiding therapies in the future.[50]

Gastrointestinal (GI) bleeding is one of the more common risks of strong antiplatelet therapy. Therefore, PPI are often prescribed as well. A recent study found, interestingly, that lower GI bleeding is more common than upper GI bleeding in patients on PPI.[51] Furthermore, the impact of PPI on the clopidogrel effect has been a matter of controversy for some time. Laboratory studies have suggested a reduced antiplatelet effect if PPI are used. However, studies looking at clinical end points have shown conflicting results. A recent systematic review provides a very good overview, including 33 studies, and concludes that clinical data are highly conflicting but that even newer, better designed studies do not show evidence of a relevant adverse effect of PPI in patients on clopidogrel regarding clinical outcomes.[52]

Sudden Cardiac Arrest

SCA is a less common but often fatal presentation of ACS.[53] While there are other reasons for SCA, especially in younger patients, the most common cause for tachyarrhythmic cardiac arrests in patients over 40 is myocardial ischaemia.[4 37] Most of these cardiac arrests occur out of hospital (out-of-hospital cardiac arrest (OHCA)). Survival for OHCA patients has been poor for several decades, averaging <10% to hospital discharge, and may be even lower, particularly in remote areas. However, in recent years survival has increased, especially in metropolitan areas. The London Ambulance Service observed an increase in survival rates from 12% to 32% between 2007 and 2012.[5]

We can only speculate about the reasons for this improvement since few single interventions have really proven to be effective.[54] It is therefore more likely that it is the combination of multiple effective treatments that is responsible for the observed improvements in survival. Early chest compressions and early defibrillation are the undisputed game changers.[55] It is likely that the availability of public automatic defibrillators, defibrillators of the EMS and public awareness, and an increasing number of lay people trained in chest compression, played major roles.[56]

However, other factors such as therapeutic hypothermia and immediate angiography to define and potentially treat the underlying cause are important as well.[57 58] An observational study of 9971 patients with OHCA of suspected cardiac cause were assessed regarding the hospital they were referred to. Those treated at hospitals with 24 h cardiac interventional services had a better survival (OR 1.40, 95% CI 1.12 to 1.74; p=0.003).

Current guidelines recommend immediate angiography in patients after successful resuscitation for an OHCA (return of a spontaneous circulation) in case of ST elevations in the postresuscitation ECG. However, the accuracy of post-resuscitation ECGs is unclear and there are grounds for recommending early angiography in all patients over 35–40 years, regardless of the ECG, if there is no obvious non-cardiac cause.

Cardiac rehabilitation after ACS

While it seems intuitive that cardiac rehabilitation programmes are beneficial by providing careful follow-up, supervised physical activity and guidance on lifestyle modification, clinical data on its effect are controversial. Very recently, cardiac rehabilitation for ACS has been challenged again by the multicentre RCT of comprehensive cardiac rehabilitation in patients following acute MI (RAMIT: Rehabilitation After Myocardial Infarction Trial).[59] In this study, cardiac rehabilitation in patients after an AMI had no effect on mortality or morbidity, cardiac medication, risk factors or lifestyle modification. However, we have to be aware that the RAMIT trial was small and if we look at the evidence more comprehensively, by pooling all available RCTs as done by a Cochrane review (combining 47 studies), there is a significant, albeit modest, effect on mortality.[60] This meta-analysis did not include the RAMIT findings which would have further reduced the estimated effect on all cause mortality from 13% to 11%.[61] It is important to note that the Cochrane review focused on physical exercise based rehabilitation, the probability being that non-exercise based rehabilitation (patient education) has little effect on mortality after MI.[62]

The problem with combining results of multiple trials is, of course, that this does not account for the 'evolution' of such interventions.[63] The results of the recent OMEGA study, which was a non-randomised cohort study, have shown that a short term comprehensive cardiac rehabilitation programme after acute MI significantly improved the 1-year prognosis.[64] Those who attended rehabilitation programmes had lower all-cause mortality than those who did not, but without randomised treatment assignment, interpretation of such data is difficult. There was a significant dose–response relationship; the more sessions attended the lower the all-cause mortality. However, low attenders were more likely to be smokers, and when adjustmentswere made for baseline differences in smoking status the dose– response association disappeared.
Though cardiac rehabilitation as currently provided in many countries may not be effective in reducing hard clinical end points, it still helps provide information, advice, and reassurance and helps in long term secondary prevention.[65]

Conclusions

The treatment options for ACS have improved significantly over the past few years, contributing to notable improvements in outcomes. This is especially the case for STEMI, while long term mortality after an NSTE-ACS is still considerable. The very recent introduction of third generation antiplatelet therapies (prasugrel, ticagrelor) and the most recent intravenous form, cangrelor, are likely to continue to improve clinical outcomes after ACS. These more potent agents can increase bleeding risks, and considering the association between bleeding and outcomes, periprocedural bleeding avoidance strategies are important. They may include radial access angiography, ultrasound guided femoral access, and the use of bivalirudin.

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Almanah 2013

Almanac 2013: cardiac arrhythmias and pacing

The national society journals present selected research that has driven recent advances in clinical cardiology.

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Abstract Important advances have been made in the past few years in the fields of clinical cardiac electrophysiology and pacing. Researchers and clinicians have a greater understanding of the pathophysiological mechanisms underlying atrial fibrillation (AF), which has transpired into improved methods of detection, risk stratification, and treatments. The introduction of novel oral anticoagulants has provided clinicians with alternative options in managing patients with AF at moderate to high thromboembolic risk and further data has been emerging on the use of catheter ablation for the treatment of symptomatic AF. Another area of intense research in the field of cardiac arrhythmias and pacing is in the use of cardiac resynchronisation therapy (CRT) for the treatment of patients with heart failure. Following the publication of major landmark randomised controlled trials reporting that CRT confers a survival advantage in patients with severe heart failure and improves symptoms, many subsequent studies have been performed to further refine the selection of patients for CRT and determine the clinical characteristics associated with a favourable response. The field of sudden cardiac death and implantable cardioverter defibrillators also continues to be actively researched, with important new epidemiological and clinical data emerging on improved methods for patient selection, risk stratification, and management. This review covers the major recent advances in these areas related to cardiac arrhythmias and pacing.

Atrial Fibrillation

Epidemiology of atrial fibrillation

A number of large scale epidemiological studies using registry databases and prospective cohort data have reported novel associations between atrial fibrillation (AF) and other non-traditional risk factors for AF. These include an increased risk of incident AF in patients with high glycosylated haemoglobin (HbA1c) and poor glycaemic control,[1] coeliac disease,[2] rheumatoid arthritis[3] and psoriasis,[4] use of non-aspirin, non-steroidal anti- inflammatory drugs (NSAIDs),[5] and increased height.[6] Another interesting association is the finding from a substudy of 260 patients with chronic AF from the SAFETY trial (Standard versus Atrial Fibrillation Specific Management Study) that mild cognitive impairment is highly prevalent among older, high risk patients hospitalised with AF.[7] In another substudy of the Cardiovascular Health Study, investigators found that higher base- line circulating concentrations of total long chain n-3 polyunsaturated fatty acids (PUFA) were asso- ciated with a lower risk of incident AF.[8]

Other interesting recent epidemiological studies on AF include the association of incident AF with an increased risk of developing end stage renal disease in patients with chronic kidney disease,[9] and a community based study of 3220 patients which showed that new AF in patients with no history of AF before a myocardial infarction increased mortality in patients with myocardial infarction.[10] In a large Swedish registry study of 100 802 patients with AF, Friberg et al[11] found that ischaemic strokes were more common in women than in men, supporting the notion that female gender should be taken into consideration when making decisions about anticoagulation treat- ment. Furthermore, among older patients admitted with recently diagnosed AF, the risk of stroke appears to be greater in women than in men, regardless of warfarin use,[12] and among healthy women new onset AF was found to be independ- ently associated with all cause cardiovascular and non-cardiovascular mortality.[13]

Medical management of AF

Data from the RealiseAF study, an international, observational, cross-sectional survey of patients with any history of AF in the previous year, sug- gested that patients in which their AF was 'con- trolled' (defined as sinus rhythm or AF with a resting heart rate ≤80 beats/min) had a better quality of life and fewer symptoms than

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those whose AF was uncontrolled.[14] Nonetheless, even patients with controlled AF experienced frequent symptoms, functional impairment, altered quality of life and cardiovascular events—hence the importance of ongoing efforts to develop novel and better treatments for AF. The RECORDAF (Registry on Cardiac Rhythm Disorders Assessing the Control of Atrial Fibrillation) registry was a worldwide, prospective observational survey of AF management in an unselected, community based cohort over a 12 months period.[15] The investigators found that in 5171 patients whose data were available, therapeutic success (driven by control of AF) was achieved in 54% overall (rhythm control 60% vs rate control 47%). The choice of rate or rhythm strategy did not affect clinical outcomes (which were driven mainly by hospitalisations for arrhythmia and other cardiovascular causes), although the choice of rhythm control reduced the likelihood of AF progression.

The RACE (Rate Control Efficacy in Permanent Atrial Fibrillation) II trial was the first formal assessment of alternative rate control goals in AF and demon- strated for the first time that a 'lenient rate control' strategy (target resting heart rate <110 beats/min) was non-inferior to a 'strict rate control' strategy (target resting heart rate <80 beats/ min and heart rate during moderate exercise <110 beats/min).[16] Two subsequent substudies of the RACE II trial showed that the stringency of rate control had no significant effect on the quality of life in patients with permanent AF[17] and that lenient rate control did not have an adverse effect on atrial and ventricular remodelling compared with strict rate control (although female gender was independently associated with significant adverse cardiac remodelling).[18] In another sub-study looking at cardio- vascular outcomes in subjects from the original AFFIRM trial (Atrial Fibrillation Follow-Up Investigation of Rhythm Management), investigators found that the composite outcome of mortality or cardiovascular hospital stays was better in rate compared with rhythm control strategies (using amiodarone or sotalol).[19] Non-cardiovascular death and intensive care unit hos- pital stay were more frequent in patients on amiodarone, and time to cardiovascular hospital stay was shorter. In a prospect- ive, randomised, open label trial of pharmacological cardiover- sion in patients with persistent AF, Yamase et al compared amiodarone with bepridil in 40 consecutive subjects.[20] The investigators found that bepridil was superior to amiodarone in achieving sinus conversion (85% vs 35%; p<0.05) and main- taining sinus rhythm after an average follow-up of 14.7 months (75% vs 50%).

The issue of whether PUFA have any beneficial effects on AF remains a topical one. A large meta-analysis of 10 randomised controlled trials involving 1955 patients found that PUFA supple- mentation had no significant effect on AF prevention.[21] In the FORWARD trial (Randomised Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation), 586 outpatient participants with confirmed symp- tomatic paroxysmal AF who required cardioversion or had at least two episodes of AF in the preceding 6 months were randomly assigned to receive placebo or PUFA (1 g/day) for 12 months.[22] The investigators found that PUFA supplementation did not reduce the recurrence of AF or have any beneficial effects on the other prespecified end points (all cause mortality, non-fatal stroke, non-fatal acute myocardial infarction, systemic embolism or heart failure). In a large placebo controlled, randomised clinical trial involving 1516 patients in 28 centres, perioperative supplementa- tion of PUFA, although well tolerated, was not shown to reduce the risk of postoperative AF.[23] In contrast, another randomised, double blind, placebo controlled trial involving 199 patients who received either PUFA (2 g/day) or placebo for 4 weeks before direct current (DC) cardioversion found that patients who received PUFA were more likely to be in sinus rhythm at 1 year follow-up compared with control patients.[24]

Monitoring and assessment of AF

The detection of paroxysmal AF can be difficult with current methods and technology; hence ongoing efforts are being made to improve methods for detection and diagnosis. The associ- ation between subclinical AF and cryptogenic stroke has gained increasing prominence with more careful monitoring of patients using invasive and non-invasive methods. In a nice study of 2580 patients aged 65 years or older with a pacemaker or defibrillator recently implanted and no history of AF, investigators detected subclinical atrial tachyarrhythmias in 261 patients (10.1%).[25] Over a mean follow-up of 2.5 years, patients with subclinical atrial tachyarrhythmias were found to have an increased risk of clinical AF and of ischaemic stroke or systemic embolism (HR 2.49, 95% CI 1.28 to 4.85; p=0.007). In

patients who do not have pacemakers or defibrillators who present with cryptogenic stroke, longer term ambulatory ECG monitoring using external or implantable devices may be worth considering to help confirm a diagnosis of subclinical AF.[26 27] In a study of 100 patients being screened for AF, investigators com- pared the effectiveness of using 7-day triggered ECG monitor- ing with 7-day continuous Holter ECG monitoring for detection of AF.[28] An arrhythmia was recorded in 42 subjects (42%) with continuous ECG recordings versus 37 subjects (32%) with triggered monitoring (p=0.56). The sensitivity of triggered ECG monitoring was found to be lower than that of continuous ECG monitoring, mainly due to a shorter effective monitoring duration, although qualitative triggered ECG ana- lysis was less time consuming than continuous ECG analysis. In another larger study of 647 patients with implantable continu- ous monitoring devices, intermittent rhythm monitoring was found to be significantly inferior to continuous monitoring for the detection of AF and was not able to identify AF recurrence in a great proportion of patients at risk.[29] In an interesting study investigating the use of N-terminal pro B-type natriuretic peptide (NT-proBNP) values to estimate the recency of AF onset and safety of cardioversion, investigators separated 86 patients presenting with presumed recent onset AF into two groups (43 in each group), based on NTproBNP concentrations above and below a cut-off value, and subjected all sub-

jects to transoesopha- geal echocardiography.[30] NT-proBNP concentrations below the cut-off value were found to be the most powerful predictor of the presence of thrombus, suggesting that a short term increase in NT-proBNP after AF onset might be useful in assessing the recency of onset of the AF episode, if unknown, and might be potentially used to help determine the safety of cardioversion.

Catheter ablation of AF

Although antiarrhythmic drugs (AADs) and catheter ablation are the main treatment options available to maintain sinus rhythm in symptomatic patients with AF, many clinicians and patients still opt for an initial conservative strategy and consider catheter ablation only after one or more AADs have been tried and found to be ineffective. The question of whether catheter abla- tion of AF is an effective initial therapy for paroxysmal AF was addressed in a small randomised study in which 294 patients (with no history of AAD use) were randomly assigned to an initial strategy with radiofrequency catheter ablation or therapy with a class 1c or III AAD.[31] The investigators found no signifi- cant difference between the ablation and drug therapy groups in the cumulative burden of AF (90th centile of arrhythmia burden 13% and 19%, respectively; p=0.10) in the initial 18 months. However, at 24 months, AF burden was significantly lower in the ablation group compared with the drug therapy group (9% vs 18%; p=0.007) and more patients in the ablation group were free from symptomatic AF (93% vs 84%; p=0.01). In the drug therapy group, 54 patients (36%) subsequently underwent ablation.

In another small randomised study of AF ablation in patients with persistent AF, advanced heart failure and severe left ven- tricular (LV) systolic dysfunction, MacDonald et al[32] found that catheter ablation was successful at restoring sinus rhythm in 50% of patients, although the procedure was associated with a significant complication rate of 15%. In addition, catheter abla- tion did not improve LV ejection fraction (LVEF) (as measured using cardiovascular magnetic resonance) or other secondary outcomes, calling into question the risk/benefit ratio of perform- ing AF ablation in patients with persistent AF and LV dysfunction. An international multicentre registry study of 1273 patients undergoing AF ablation suggested that maintenance of sinus rhythm through catheter ablation was associated with a lower risk of stroke and death compared with a control group consisting of medically treated patients with AF in the Euro Heart Survey.[33]

Several studies have recently been reported which increase our understanding of the factors associated with success or failure following AF ablation. The importance of pulmonary vein (PV) isolation was further reinforced by Miyazaki et al[34] who reported long term clinic outcomes of 83.6% (480 out of 574 patients) with a mean follow-up of 27±14 months using an extensive PV isolation approach in patients with both paroxys- mal and persistent AF.[34] Late recurrences (defined as 6– 12 months following the initial AF ablation procedure) was asso- ciated with PV reconnection in all patients, while very late recurrences (>12 months after the procedure) were associated with non-PV triggers in 85.7% of cases. The added benefit of performing additional linear ablation lines after PV isolation on improving outcomes following AF ablation has been further questioned in a prospective, randomised study of 156 patients with paroxysmal AF who were randomly assigned to undergo

PV isolation only, PV isolation and a roof line, or PV isolation, roof line and a posterior inferior line.[35] The investigators found no improvement in clinical outcome in the patients who received the additional lines while, unsurprisingly, the addition of the linear ablations significantly prolonged procedure times. A number of investigators have found that many factors are pre- dictive of or adversely related to outcome following AF ablation in addition to well established factors, such as type of AF (paroxysmal or persistent), left atrial size, and presence of LV dysfunction. These novel factors include cardiac related factors, such as atrial electromechanical interval on pulse wave Doppler imaging[36] and left atrial fibrosis as assessed by measuring echo- cardiograph derived calibrated integrated backscatter,[37] pericar- dial fat,[38] plasma biomarkers (such as plasma B-type natriuretic peptide values[39]), renal dysfunction,[40] and the metabolic syn- drome.[41] Interestingly, the presence of dissociated PV potentials, often used as a marker of successful PV isolation, was not found to predict AF recurrence in a study of 89 consecutive patients over a mean follow-up of 21±8 months.[42] In a small rando- mised controlled study of 161 patients, a 3 month course of col- chicine (0.5 mg twice daily) was found to decrease early AF recurrence after PV isolation, probably due to a reduction in inflammatory mediators, including interleukin 6 (IL-6) and C reactive protein (CRP).[43] Colchicine (1.0 mg twice daily initially followed by a maintenance dose of 0.5 mg twice daily for 1 month) was also found to reduce the incidence of post- operative AF and decrease in-hospital stay in a multicentre, double blind, randomised trial of 336 patients.[44] In an interest- ing small randomised study of PV isolation with and without concomitant renal artery denervation in 27 patients with refrac- tory symptomatic AF and resistant hypertension, Pokushalov et al showed that renal artery denervation reduced systolic and diastolic blood pressure and reduced the recurrence of AF during 1 year follow-up.[45]

Another area of research in the field of AF ablation has been on the factors associated with increased complications from the procedure. Using data from the California State Inpatient Database, Shah et al found that among 4156 patients who underwent an initial AF ablation procedure, 5% had periproce- dural complications (most commonly vascular) and 9% were readmitted within 30 days.[46] Factors associated with a higher risk of complications and/or 30-day readmission following an AF ablation were older age, female sex, prior AF hospitalisations, and recent hospital procedure experience. In another retrospective study of 565 patients, both the CHADS2 and CHA2DS2-VASc scores were found to be useful predictors of adverse events following AF ablation.[47]

The first randomised clinical trial comparing the efficacy and safety of catheter ablation of AF with surgical abla-

tion involved 124 patients with drug refractory AF.[48] The investigators found that the primary end point (freedom from left atrial arrhythmia
>30 s without AADs after 12 months) was 36.5% for the cath- eter ablation group and 65.6% for the surgical group (p=0.0022), but patients in the surgical group experienced sig- nificantly greater adverse effects (driven mainly by procedural complications) compared to the catheter ablation group. Pison et al reported relatively high 1 year success rates (93% for par- oxysmal AF and 90% for persistent AF) with a combined trans- venous endocardial and thorascopic epicardial approach for a single AF ablation procedure in a small cohort of 26 patients with AF.[49]

Strategies to decrease thromboembolism

The use of novel oral anticoagulants to decrease the risk of stroke and systemic thromboembolism in patients with AF has gained increasing use and acceptance over the past several years following the publication of a number of landmark multicentre, randomised clinical trials comparing their efficacy with conven- tional vitamin K antagonists.[50–53] A meta-analysis of 12 studies totalling 54 875 patients showed a significant reduction of intra- cranial haemorrhage with these novel anticoagulants compared with vitamin K antagonists, and a trend toward reduced major bleeding.[54] These novel oral anticoagulants may also have a role in patients undergoing DC cardioversion. A sub-study of patients with AF who underwent cardioversion in the RE-LY (Randomised Evaluation of Long-Term Anticoagulation Therapy) trial showed that dabigatran (at two doses of 110 and 150 mg twice daily) is a reasonable alternative to warfarin, with low frequencies of stroke and major bleeding within 30 days of cardioversion.[55]
These novel oral anticoagulants may also have a role to play in the periprocedural anticoagulation of patients undergoing radiofrequency ablation for AF. Several registry and observa- tional studies have suggested that dabigatran is as safe as peri- procedural warfarin in patients undergoing AF ablation,[56–58] although one study suggested an increased risk of bleeding and thromboembolic complications with dabigatran compared with warfarin.[59] A prospective randomised controlled trial is required to definitively address the issue as to whether these novel oral anticoagulants can be used in place of warfarin for periproce- dural anticoagulation in patients undergoing AF ablation. Economic evaluation of these novel oral anticoagulants suggest that they may be cost effective as a first line treatment for the prevention of stroke and systemic embolism,[60] especially in patients at high risk of haemorrhage or stroke, unless inter- national normalised ratio (INR) control with warfarin is already excellent.[61]
Another strategy to decrease thromboembolic events in patients with AF that is gaining favour involves the use of mech- anical left atrial appendage (LAA) occlusion devices. In a system- atic review of 14 studies, implantation of LAA occlusion devices in patients with AF was successful in 93% of cases, with peri- procedural mortality and stroke rates of 1.1% and 0.6%, respectively; the overall incidence of stroke among all studies was 1.4% per annum.[62] A substudy of the PROTECT AF
(Percutaneous Closure of the LAA versus Warfarin Therapy for Prevention of Stroke in Patients with AF) study reported that 32% of implanted patients had some degree of peri-device flow at 12 months on transoesophageal echocardiography, although this did not appear to be associated with an increased risk of thromboembolism compared to patients with no peri-device flow who discontinued warfarin.[63] A systematic review aimed at determining which subgroups of patients would benefit most from LAA closure devices looked at the location of atrial thrombi in patients with AF in a total of 34 studies.[64] The inves- tigators concluded that patients with non-valvular AF may derive greater benefit from LAA closure devices—56% of patients with valvular AF had atrial thrombi located outside the LAA, 22% in mixed cohorts and 11% in non-valvular AF patients.

Cardiac Resynchronisation Therapy and Pacing

Cardiac resynchronisation therapy

Recent research in the area of cardiac resynchronisation therapy (CRT) has looked at the long term effects of CRT pacing on LV and right ventricular (RV) function and further into which sub- groups of patients may derive greatest benefit from CRT pacing. A favourable RV functional response to CRT appears to be associated with improved survival in patients with CRT devices, and RV function was found to be an independent predictor of long term outcome after CRT insertion in a study of 848 CRT recipients.[65] Following the landmark MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronisation Therapy) study, which demonstrated that CRT combined with implantable cardioverter defibrillator (ICD, CRT-D) decreased the risk of heart failure events in relatively asymptomatic patients with a low ejection fraction and wide QRS complexes,[66] a number of subsequent analyses have provided further interesting information. This includes data on the benefits of CRT in reducing the risk of recurring heart failure events[67] and atrial arrhythmias,[68] identifica- tion of additional factors that are associated with improved response to CRT[69 70] and with a super-response (defined by patients in the top quartile of LVEF change),[71] factors associated with greatest improvement in quality of life,[72] and information on optimal lead positioning of the LV lead.[73 74]
In a prospective, randomised controlled study to address whether ventricular dyssynchrony on echocardiography pre- dicted response to CRT, Diab et al found that the presence of echocardiographic dyssynchrony identified patients who derived the most improvement from CRT, although patients without dyssynchrony also showed more benefit and less deterioration with CRT than without. The authors concluded that the latter group of patients should not be denied CRT.[75] CRT appeared to produce some benefits in patients with heart failure and a normal QRS duration, with patients experiencing an improve- ment in symptoms, exercise capacity and quality

of life, although there was no difference in total or cardiovascular mor- tality in patients who received CRT compared with those receiv- ing optimal pharmacological management.[76] Among patients with heart failure and prolonged QRS duration who received a CRT device, those with a left bundle branch block (LBBB) morphology derived greater benefit (lower risk of ventricular arrhythmias and death and improved echocardiographic parameters) compared with patients who had a non-LBBB QRS pattern (right bundle branch block (RBBB) or intraventricular conduction disturbances).[77]

The issue of whether CRT in patients undergoing atrioven- tricular (AV) junction ablation for permanent AF was superior to conventional RV pacing in reducing heart failure events was addressed in a prospective, randomised, multicentre study involving 186 patients.[78] Over a median follow-up of 20 months (IQR 11–24 months) fewer patients in the CRT group (11%) experienced primary end point events (death from heart failure, hospitalisation due to heart failure or worsening heart failure) compared with patients in the RV group (26%; CRT vs RV group: sub-hazard ratio (SHR) 0.37, 95% CI 0.18 to 0.73; p=0.005). Total mortality was similar in both groups. In a follow-up analysis looking at the predictors of clinical improvement after the 'ablate and pace' strategy, more patients in the CRT group responded to treatment (83% vs 63% in the RV group).[79] CRT mode and echo-optimised CRT were found to be the only independent protective factors against non- response (HR=0.24, 95% CI 0.10 to 0.58, p=0.001 and HR=0.22, 95% CI 0.07 to 0.77, p=0.018, respectively). In the PACE (Pacing to Avoid Cardiac Enlargement) trial, RV pacing in patients with bradycardia and preserved LVEF was associated with adverse LV remodelling and deterioration of systolic func- tion at the second year, which was prevented by biventricular pacing.[80]

Heart block and pacemakers

The long term survival of older patients (average age 75 ±9 years) with Mobitz I second degree AV block was examined in a retrospective cohort study of 299 patients.[81] The investiga- tors found that 141 patients (47%) had a cardiac implantable electronic device (CIED) inserted during the follow-up period, of which 17 were ICDs. Patients with a CIED had greater cardiac comorbidity than those without a CIED, although CIED implantation was associated with a 46% reduction in mortality (HR 0.54, 95% CI 0.35 to 0.82; p=0.004). In another observational study of the impact of the ventricular pacing site on LV function in children with AV block, van Geldrop et al found that LV fractional shortening was significantly higher with LV pacing than with RV pacing.[82]

Further research on the topic of whether cardiac pacing is beneficial in patients with neurally mediated syncope suggests that dual chamber pacing may be useful in patients with severe asystolic forms. In the randomised multicentre ISSUE-3 trial (Third International Study on Syncope of Uncertain Aetiology) patients with syncope due to documented asystole on an implantable loop recorder were randomly assigned to dual chamber pacing with rate drop response or to sensing only.[83] Those assigned to dual chamber pacing had fewer syncopal episodes during follow-up (32% absolute and 57% relative reduc- tion in syncope). A positive test with intravenous adenosine 5^0-triphosphate (ATP) has been shown to correlate with a subset of patients with neurally mediated syncope.[84] A randomised, multicentre trial of the potential benefit of the ATP test in elderly patients (mean age 75.9±7.7 years) with syncope of unknown origin reported that active dual chamber pacing in those with a positive ATP test reduced syncope recurrence risk by 75% (95% CI 44% to 88%).[85] Long term outcome data on a distinct form of AV block, paroxysmal AV block, which cannot be explained by currently known mechanisms, suggest that these patients have a long history of recurrent syncope and may benefit from cardiac pacing, although in a small series of 18 patients (followed up for up to 14 years), no patient had per- manent AV block.[86] The prognosis among healthy individuals admitted with their first episode of syncope was studied in a Danish nationwide registry involving 37 017 patients with syncope and 185 085 age and sex matched controls.[87] Patients who were admitted with syncope had significantly increased all cause mortality, cardiovascular hospitalisation, recurrent syncope and stroke event rates and were more likely to have a pacemaker or ICD inserted later.

CIED related infection

CIED infection is recognised as a significant cause of morbidity, mortality, and increased healthcare costs. The clinical character- istics, outcome, and health care implications of CIED related infections and endocarditis was analysed in a prospective cohort study using data from the International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCE) involving 61 centres in 28 countries.[88] CIED infection was diagnosed in 177 out of 2760 patients (6.4%). In-hospital and 1 year mortality rates were 14.7% (95% CI 9.8% to 20.8%) and 23.2% (95% CI 17.2% to 30.1%), respectively. The rate of concomitant valve infection was high (found in 66 patients, 37.3%, 95% CI 30.2% to 44.9%) and early device removal was associated with improved survival at 1 year. In an attempt to assess the long term outcomes and predictors of mortality in patients treated according to current recommendations for CIED infection, Deharo et al conducted a two-group matched cohort study of 197 cases of CIED infection.[89] Long term mortality rates were similar between cases and matched controls (14.3% vs 11.0% at 1 year and 35.4% vs 27.0% at 5 years, respectively; both p=NS). Independent predictors of long term mortality were older age, CRT, thrombocytopenia, and renal insufficiency. In another study examining whether the timing of the most recent CIED procedure influenced the clinical presentation and outcome of lead associated endocarditis (LAE), investigators found that early LAE presented with signs and symptoms of local pocket infection, whereas a remote source of bacteraemia was present in 38% of late LAE but only 8% of early LAE.[90] In-hospital mortality was low (early 7%; late 6%).

Ventricular Arrhythmias and Sudden Cardiac Death

Epidemiology of sudden cardiac death

Sudden death is a frequent and well recognised risk in patients following myocardial infarction. In a study analysing data from 1067 patients from VALIANT (Valsartan in Acute Myocardial Infarction Trial) who had sudden death, investigators found that a high proportion of the deaths occurred at home, although in-hospital events were more common early on.[91] Patients who were asleep were more likely to have unwitnessed events. Although sudden cardiac death (SCD) and coronary artery disease (CAD) have many risk factors in common, certain clin- ical and electrocardiographic parameters may be useful to help separate out the two risks. For example, in a study of 18 497 participants from the ARIC (Atherosclerosis Risk in Communities) study and the Cardiovascular Health Study, Soliman et al found that after adjusting for common CAD risk factors, hypertension, increased heart rate, QTc prolongation, and abnormally inverted T waves were found to be stronger pre- dictors of high SCD risk.[92] In comparison, elevated ST segment height (measured at both the J point and 60 ms after the J point) was found to be more predictive of high incident CAD risk.

More research has also been performed on SCD in other sub- groups. In a prospective, national survey of sports related sudden death performed in France from 2005 to 2010, involv- ing subjects 10–75 years of age, investigators found that the overall burden of sudden death was 4.6 per million population per year, with 6% of cases occurring in young competitive ath- letes and more than 90% of cases occurring in the context of recreational sports.[93] Bystander cardiopulmonary resuscitation (CPR) and initial use of cardiac defibrillation were the strongest independent predictors for survival to hospital discharge, although bystander CPR was only initiated in one third of cases. In a retrospective autopsy study of 902 young adults (mean age 38±11 years) who had suffered non-traumatic sudden death, the cause of sudden death was attributed to a cardiac condition in 715 (79.3%) and unexplained in 187 (20.7%).[94] In another nationwide study on the incidence of SCD in persons aged 1–35 years, 7% of all deaths were attributed to SCD.[95] The inci- dence of SCD in the young, estimated to be 2.8% per 100 000 person-years, was higher than previously reported. Risk factors for SCD in post-menopausal women may include more novel parameters, such as higher pulse, higher waist-to-hip ratio, ele- vated white blood cell count, and ethnicity (African Americans having a higher risk) as well as traditional risk factors.[96]

More intense research has been conducted in a variety of set- tings on the early repolarisation syndrome (ERS) since landmark studies showed a link with idiopathic ventricular fibrillation and sudden death.[97 98] These include studies on ERS on cardiac arrest survivors with preserved ejection fraction,[99] in families with sudden arrhythmic death syndrome[100] and other families with an early repolarisation pattern on the ECG,[101] and in Asian populations.[102] However, there is still some controversy over the exact clinical significance of these ECG findings and what the implications are.[103 104]

The genetics of inherited cardiac conditions and how specific genotypes can lead to clinical manifestations of disease, affect SCD risk or guide management continues to attract intense interest.[105–108] Results from the DARE (Drug-induced Arrhythmia Risk Evaluation) study, in which 167 single nucleo- tide polymorphisms spanning the NOS1AP gene, were evaluated in 58 Caucasian patients who had experienced drug induced QT prolongation and 87 Caucasian controls, demonstrated that common variations in the NOS1AP gene were associated with a significant increase in drug induced long QT syndrome.[109] This may have clinical implications for future pharmacogenomics testing in patients at risk of drug induced long QT syndrome and safer prescribing. In another study assessing whether non- cardiovascular hERG (human Ether à go-go-Related Gene) channel blockers are associated with an increased risk of SCD in the general population, investigators compared 1424 cases of SCD with 14 443 controls.[110] Use of hERG channel blockers was found to be associated with an increased risk of SCD and drugs with a high hERG channel inhibiting capacity had a higher risk of SCD than those with a low hERG channel inhibit- ing capacity.

Implantable cardioverter defibrillators

The clinical parameters associated with death before appropriate ICD therapy in patients with ischaemic heart disease who had an ICD inserted for primary prevention were assessed in a retro- spective cohort study of 900 patients.[111] The investigators found that New York Heart Association (NYHA) functional class ≥ III, advanced age, diabetes mellitus, LVEF ≤25%, and a history of smoking were significant independent predictors of death without appropriate ICD therapy, and suggested that this information may facilitate a more patient tailored risk estima- tion. Another risk score for predicting acute procedural compli- cations or death after ICD implantation using 10 readily available variables from 268 701 ICD implants was developed to provide useful information in guiding physicians on patient selection and determining the intensity of post-implant care required.[112] A risk score aimed at predicting the long term (8 years) benefit of primary prevention ICD implantation was applied to 11 981 patients from the MADIT-II trial.[113] The investigators found that patients with low and intermediate risk (0 or 1–2 risk factors, respectively) benefitted more from ICD implantation, compared with patients with high risk (≥3 risk factors) who had multiple comorbidities, in which there was no significant difference in 8 years survival between ICD and non-ICD recipients.

Another risk score for the prediction of mortality in Medicare beneficiaries receiving ICD implantation for primary prevention was developed from a cohort of 17 991 patients and validated in a cohort of 27 893 patients.[114] Over a median follow-up of 4 years, 6741 (37.5%) patients in the development cohort and 8595 (30.8%) patients in the validation cohort died. Seven

clinically relevant predictors of mortality were identified and used to develop a model for determining those patients at highest risk for death after ICD implantation. Future selection of ICD recipients for primary prevention ICDs may therefore be refined and more personalised to the individual patient's risk/ benefit profile with the use of such models, rather than being based predominantly on LVEF, as is recommended by current guidelines.

Other investigations, such as cardiac magnetic resonance (CMR) imaging to identify and characterise myocardial scar, may be a useful addition to future risk stratification of patients for primary prevention ICD implantation. The ability of scar characteristics assessed on CMR to predict ventricular arrhyth- mias was evaluated in a study of 55 patients with ischaemic car- diomyopathy who received an ICD for primary prevention and in whom CMR with late gadolinium enhancement had been performed before ICD implantation.[115] All CMR derived scar tissue characteristics were found to be predictive for the occur- rence of ventricular arrhythmias, supporting the potential use of this imaging modality to help refine risk stratification of patients and improve selection for ICD implantation. This finding was further supported by a prospective study of 137 patients evaluated with CMR before ICD implantation for primary preven- tion.[116] Myocardial scarring on CMR was found to be an independent predictor of adverse outcomes. Patients with sig- nificant scarring (>5% of the left ventricle) with LVEF >30% had a similar risk to those with LVEF ≤30%, while in patients with LVEF ≤30%, minimal or no scarring was associated with low risk, similar to those with LVEF >30%.

The use of intracardiac ICD parameters to assess risk has also received further attention. In a prospective, multicentre study of 63 ICD patients, T wave alternans and non-alternans variability (TWA/V) was found to be significantly greater before ventricular tachycardia/ventricular fibrillation (VT/VF) episodes than during baseline rhythm.[117] The investigators suggested that continuous measurements of TWA/V from the intracardiac ICD electro- grams may be a useful parameter to detect impending VT/VF and allow the device to initiate pacing therapies to prevent the ventricular arrhythmias from occurring. In contrast, an early analysis of a prospective, single centre study on the use of ICD based ischaemia monitoring on clinical care and patient manage- ment reported that this parameter was not clinically useful and actually increased the number of unscheduled outpatient visits in patients with this feature on their ICD compared with patients with ICDs without this capability.[118]

Reports on the complications and negative aspects of ICDs include problems associated with the Sprint Fidelis ICD leads[119–121] and potential psychological impact and phobic anxiety among ICD recipients.[122] In a study of 3253 patients from 117 Italian centres who underwent de novo implantation of a CRT-D device, investigators found that device related events were more frequent in patients who received CRT-D devices compared with those who received ICDs only (single or dual chamber), although these events were not associated with a worse clinical outcome.[123] In a multicentre, longitudinal cohort study of 104 049 patients receiving single and dual chamber ICDs, dual chamber device implantation was more common, but was associated with increased peri-procedural complications and in-hospital mortality compared with single chamber ICDs.[124] A retrospective, single centre cohort study of 334 hypertrophic cardiomyopathy patients with ICDs reported that this group of patients had significant cardiovascular mortality and were exposed to frequent inappropriate shocks and implant complications.[125] Adverse ICD related events (inappropriate shocks and/or implant complications) were seen in 101 patients (30%; 8.6% per year), and patients with CRT-D were more likely to develop implant complications than those with single chamber ICDs and had a higher 5-year cardiovascular mortality rate.

Strategies to reduce ICD complications and inappropriate shocks include using special diagnostic ICD algorithms to iden- tify potential lead problems early,[126] and changes in ICD pro- gramming with a prolonged delay in therapy for tachyarrhythmias of ≥200 beats/min or higher, as demonstrated in the MADIT-RIT (MADIT-Reduction in Inappropriate Therapy) trial.[127] Increasing clinical experience is also being gained in the use of subcutaneous ICDs,[128 129] which holds great potential in reducing some types of ICD related complica- tions, although an initial learning curve needs to be overcome first. Real world data of ICD implantation and use show that patients treated by very low volume operators (physicians who implanted ≤1 ICDs per year) were more likely to die or experi- ence cardiac complications compared with operators who fre- quently performed ICD implantation.[130] Another strategy to reduce ICD complications is to improve the selection process of those patients who would truly benefit from these devices. In an observational outcome study of consecutive subjects referred to a regional inherited cardiac conditions clinic because of a rela- tive who had sudden unexpected death, the number of ICDs inserted as a result of specialist assessment was found to be very small (2%).[131]

Out-of-hospital cardiac arrest

Survival from out-of-hospital cardiac arrest (OHCA) appears to have increased over the past several years, probably as a result of better pre-hospital care (early recognition, more effective CPR, faster emergency services response) and advances in the hospital management of patients following OHCA.[132 133] Data from the London Ambulance Service's cardiac arrest registry from 2007 to 2012 showed an improvement in OHCA survival over the 5 year study period.[134] In an observational Swedish registry study of 7187 patients with OHCA over an 18 year period, bystander CPR was found to increase from 46% to 73% (95% CI for OR 1.060 to 10.081 per year), early survival increase from 28% to 45% (95% CI 1.044 to 1.065), and survival to 1 month increase from 12% to 23% (95% CI 1.058 to 1.086).[135] Strong predictors of early and late survival were a short interval from collapse to defibrillation, bystander CPR, female gender,

and place of collapse. A large prospective cohort study of OHCA in North American adults involving 12 930 subjects (2042 occurring in a public place and 9564 at home) also found that the rate of survival to hospital discharge was better for arrests in public settings with automated external defi- brillators (AEDs) applied by bystanders compared to those that occurred at home (34% vs 12%, respectively; adjusted OR 2.49, 95% CI 1.03 to 5.99; p=0.04).[136] Hospital characteristics asso- ciated with improved patient outcomes following OHCA were analysed from the Victorian Ambulance Cardiac Arrest Registry of 9971 patients over an 8 year period.[137] Outcome following OHCA was found to be significantly improved in hospitals with 24 h cardiac interventional services (OR 1.40, 95% CI 1.12 to 1.74; p=0.003) and patient reception between 08.00 and 17.00 h (OR 1.34, 95% CI 1.10 to 1.64; p=0.004). OHCA in children was assessed in a prospective, population based study of victims younger than 21 years of age.[138] The incidence of paediatric OHCA was 9.0 per 100 000 paediatric person-years (95% CI 7.8 to 10.3), whereas the incidence of paediatric OHCA from cardiac causes was 3.2 (95% CI 2.5 to 3.9). The authors concluded that OHCA accounts for a significant propor- tion of paediatric mortality, although the vast majority of OHCA survivors have a neurologically intact outcome.

Studies on the optimal sequence of CPR measures to use in OHCA patients have reported varying results. In a meta-analysis of four randomised controlled clinical trials enrolling 1503 sub- jects with OHCA, no significant difference was found between chest compression first versus defibrillation first in the rate of return of spontaneous circulation, survival to hospital discharge or favourable neurologic outcomes, although subgroup analyses suggested that chest compression first may be beneficial for cardiac arrests with a prolonged response time.[139] In a more recent, nationwide, population based observational study involv- ing OHCA patients in Japan who had a witnessed arrest and received shocks with public access AED, compression only CPR was found to be associated with a significantly higher rate of survival at 1 month and more favourable neurological outcomes compared with conventional CPR measures (chest compression and rescue breathing).[140] However, for children and younger people who have OHCA from non-cardiac causes, and in

people in whom there was a delay in starting CPR, other studies have suggested that conventional CPR is associated with better outcomes than chest compression only CPR.[141 142]

Conclusions

Important progress has been made over the past few years in our understanding of basic and clinical cardiac electrophysiology which have advanced and improved the management of patients with heart rhythm disorders. Multiple studies have demon- strated an association between AF and various systemic condi- tions and novel risk factors. These studies highlight the importance and complexity of this complex arrhythmia and further support the notion that AF is a systemic condition. Although many of these associations have not been shown to play a causal role, they may nonetheless prove useful clinically in future risk stratification scores for the diagnosis or treatment of AF. More research is still needed to increase our understand- ing of the underlying mechanisms responsible for the develop- ment and progression of AF and which patient subgroups will benefit most from specific treatments or the different options for anticoagulation.

The field of CRT and pacing has also progressed rapidly over the past few years with a lot of interest in the optimal clinical parameters for selection of patients, prediction of response, and adverse remodelling. Similarly, as our understanding of the sub- strate responsible for ventricular arrhythmias and SCD improves, the selection of suitable candidates for ICD therapy is becoming more refined. Research into the complications asso- ciated with implantable cardiac devices, such as device infection and inappropriate shocks from ICDs, remains important as indi- cations for device implantation continue to expand and more and more patients with existing devices undergo device replace- ment procedures.

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Almanah 2013

Almanac 2013: heart failure

The national society journals present selected research that has driven recent advances in clinical cardiology.

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Epidemiology, The National Audit and Guidelines

The National Heart Failure Audit continues to be an invaluable resource for understanding how acute heart failure is managed in England and Wales. The most recent report1 describes just over 37 000 hospitalisations. As in previous publications, fewer than half the patients were managed in cardiology wards, yet those who were had a better outcome; half were referred at discharge to cardiologists for follow-up and they, too, had a better outcome. An innovation in the audit this time was the publication of hospital level analysis. It would be invidious to pick out names, but it is very striking how variable are the rates of such basic items as the use of echocardiography, availability of a cardiologist to manage the patients and the rate of prescription of different drugs.

Studies show that, during long-term follow-up, patients managed by heart failure specialists including 'heart failure nurses' are more likely to be treated with the appropriate medication in the appropriate dose, have lower (re-)admission rates to hospital and a better prognosis.[2] There is reasonable evidence that there are better outcomes if part of the multidisciplinary intervention is made in the home.[3] There is strong evidence that specialist clinics reduce the risk of readmission with heart failure immediately after an index admission.[4]

Also available to the clinician are the heart failure guidelines from the National Institute for Health and Care Excellence (NICE)[5 6] and the associated quality standards.[7] The NICE standards make it clear what NHS services across England and Wales should be striving towards. Combined with the hospital level analysis from the audit, the quality standards should give clinical teams the ammunition they need when discussing their heart failure service with management teams in both primary and secondary care.

However, it is becoming ever clearer that the systems used for managing heart failure at present are unlikely to be adequate in future: a study from the USA[8] predicts that the costs of managing heart failure will more than double by 2030, mainly due to the ageing of the population. The capacity of the health service to accommodate the increasing numbers is not infinite. Part of the solution will surely have to be a change towards greater efficiency of use of limited resources, but reducing the risk of developing heart failure will also be a major contributor. Of some relief to many doctors, coffee appears to offer some protection![9]

The latest guidelines from the European Society of Cardiology were published in 2012, merging the management of acute and chronic heart failure.[10] They continue to emphasise the central role of natriuretic peptide testing for diagnosis—which is still not universally available in the UK but a key part of the NICE recommendations. The guidelines emphasise that mineralocorticoid receptor antagonists should now be considered to be part of standard therapy for anyone with symptomatic heart failure and should be used in preference to angiotensin receptor blockers as add-on therapy ACE inhibitors and β blockers.

Acute Heart Failure

For many years the focus of heart failure research has been on patients with chronic stable heart failure. There has been little new for acute heart failure for many years. Recruiting patients with acute heart failure is difficult: they present acutely, often in the middle of the night, and are often extremely unwell. However, clinical trials are now reporting which are starting to challenge the 'standard' management of acute heart failure.

Common precipitants of an admission to hospital with heart failure include intercurrent illness, an ischaemic event or an arrhythmia. Lists of precipitants often quote 'environment' without specifying further what that might mean; but now we have some hard evidence. In a meta-analysis, Shah and colleagues[11] found very strong relations between the risk of both hospitalisation for heart failure and

death and many environmental pollutants including carbon monoxide, sulfur dioxide, nitrogen dioxide and particulate matter. There is a clear public health interest in reducing environmental pollution, and we can now see the economic consequences of pollution in terms of heart failure admissions.

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Fluid management

Data from the national audit suggest that around half of patients admitted to hospital with heart failure have moderate or severe fluid retention. Traditional management has been by fluid restriction (often with salt restriction), but there is remarkably little evidence to show that this treatment is effective. In a small but intriguing study, Aliti et al[12] randomised 75 patients to a radical fluid-restricted (800 mL/day) and sodium-restricted (800 mg/day) regime versus no such restriction. There was no effect of the restricted diet on clinical outcomes (particularly weight loss and readmission rates at 30 days), but the fluid restriction led to greater thirst. While this is certainly not definitive evidence, it does challenge standard practice and should lead to larger trials.

The standard therapy for fluid retention is intravenous diuretic use, often using infusions over several days. It might be possible to use ultrafiltration to remove fluid more rapidly, and an early trial of 200 patients suggested that ultrafiltration might reduce the need for emergency attendances with heart failure up to 3 months after discharge compared with standard therapy.[13] In CARRESS-HF, however, the effects of ultrafiltration in 188 patients with the combination of fluid retention due to heart failure and worsening renal failure were studied. The primary endpoint was creatinine and weight loss at 96 h. Perhaps surprisingly, renal function deteriorated more in the ultrafiltration group than with standard therapy. There was no difference between the groups in either mortality or 90-day readmission rate.

It is difficult to know how to interpret these data. The patients in CARESS-HF differed from those in UNLOAD, being at much higher risk because of their renal failure at baseline. Despite the patients at trial entry having 'persistent congestion' and worsening renal function (mean creatinine at trial entry 180 µmol/L), those randomised to standard therapy lost over 4 kg in weight with no change in creatinine at 96 h. Those randomised to ultrafiltration had a similar weight loss. It may simply be that the rise in creatinine of around 20 µmol/L with ultrafiltration represented haemoconcentration rather than reflecting any significant change in renal function. Ultrafiltration holds out the hope of more rapid removal of fluid for patients with heart failure (the median length of stay for fluid retention remains around 11 days), but its precise role has still not been defined.

Relaxin

There has been much excitement about serelaxin, human recombinant relaxin-2. Relaxin is mainly known for its effect in pregnancy, but it causes arterial vasodilation with little effect on venodilation. A small dose-finding trial suggested that it might lead to more rapid relief of breathlessness in patients with acute heart failure, with a suggestion that it might improve outcome.[14] In the RELAX-AHF trial,[15] 1161 patients with acute heart failure were randomised to receive 48 h infusions of placebo or serelaxin. The serelaxin-treated patients had a modest improvement in their breathlessness, but only in one of the two scales used. More interestingly, though, there was a reduction in mortality at 6 months in the serelaxin group compared with placebo.

How this will translate into clinical practice is not at all clear. Although the Food and Drug Administration in the USA has given serelaxin 'Breakthrough Therapy' designation,[16] suggesting that they believe serelaxin represents 'a substantial improvement over currently available therapies', the data from RELAX-AHF are not convincing. There were only a small number of events, serelaxin appeared to have no effect on other events, and the comparator limb of the trial was placebo (and not another vasodilator such as a nitrate). Nevertheless, if the results are confirmed in further trials, serelaxin may represent the first major step forward in treating acute heart failure in many years.

Neprilysin inhibition

LCZ696 is the first in a new class of drugs termed ARNIs—that is, a combined angiotensin II receptor antagonist (valsartan) with a neprilysin inhibitor. Neprilysin is the enzyme responsible for the breakdown of natriuretic peptides, so its blockade increases the amount of natriuretic peptide in the circulation. In the PARAMOUNT trial,[17] 301 patients with heart failure and a normal ejection fraction were randomised to receive the combined inhibitor or valsartan alone. Those receiving LCZ696 had a greater decline in N-terminal prohormone of brain natriuretic peptide at 12 weeks (an effect lost by 36 weeks), and there was greater improvement in symptoms. The positive results will probably trigger a large outcome study, although there will be problems in knowing what the comparator to LCZ might be.[18]

Levosimendan

The REVIVE studies testing the effects of levosimendan in patients with acute heart failure have finally been published, around 8 years after they were first presented.[19] Levosimendan is a calcium sensitising drug—it has inotropic and vasodilator effects. There was much initial enthusiasm over its possible role in acute heart failure and, in REVIVE, there was a greater likelihood of clinical improvement with levosimendan. However, there was an increased risk of death, albeit non-significant, in the levosimendan group.

The delay in publication highlights a very important issue in clinical trials—namely, that neutral or negative trials might go unreported. Levosimendan has been widely available in Europe, but its potentially deleterious effects may not be recognised by those using it. Those designing and running clinical trials have a moral obligation to publish their data: patients have, after all, agreed to take part in clinical trials on the basis that the results may benefit others.[20]

Chronic Heart Failure

Ivabradine

The SHIFT study[21] suggested that the addition of ivabradine, which slows the heart rate by inhibiting sinus

node depolarisation, improves outcomes in patients with heart failure due to left ventricular systolic dysfunction, in sinus rhythm and with a heart rate ≥70/min. The benefit seen was largely a reduction in hospitalisation for heart failure, but a post hoc analysis suggested that there may be a survival benefit for patients with a resting heart rate ≥75/min.[22]

A single technology assessment of ivabradine by NICE[23] [24] recommends ivabradine as an adjunct for patients with a resting heart rate ≥75/min who are already on standard therapy (including appropriate β blocker at the maximally tolerated dose), but goes on to suggest that ivabradine should only be started by a heart failure specialist. The need for a specialist goes some way to addressing the major concern that ivabradine might come to be seen as an acceptable alternative to β blockers when the evidence that β blockers improve survival is overwhelming.

The ivabradine discussion highlights the potential importance of heart rate reduction as a therapeutic target. A challenging reinterpretation of the data from the DIG trial suggests that digoxin in patients with heart failure in sinus rhythm had a similar reduction in the endpoint used in the SHIFT study (namely, cardiovascular death or hospitalisation for heart failure) as ivabradine, with the effect being a reduction in hospitalisation rather than an increase in survival.[25] Although digoxin is very variably used nowadays, it may be that we should be revisiting its use as heart rate-reducing agent.

Aliskiren

Inhibition of the renin-angiotensin-aldosterone system (RAAS) has been the cornerstone of heart failure management for decades but, although the outlines of the system are well known, the full ramifications of the RAAS are still being uncovered. For example, angiotensin II (Ang II) can be broken down by ACE2 to yield Ang1–7, which itself has biological activity.[26] There are many potential targets for treatment becoming available. One potential target has been the initial step in the cascade
—inhibition of the enzymatic activity of renin itself. Aliskiren is a direct renin inhibitor. Early work suggested that it might have a more profound effect on suppressing natriuretic peptide production than standard therapy,[27] and its ability to avoid any escape from ACE inhibition makes it an attractive agent. However, two trials have cast doubt on its effectiveness. In the ALTITUDE trial,[28] 8561 patients with diabetes, chronic kidney disease, cardiovascular disease or both were randomised to receive aliskiren or placebo in addition to standard therapy. The trial was stopped early after an interim efficacy analysis, and there was a suggestion (although not statistically significant) that aliskiren might be harmful. In the ASTRONAUT study,[29] [30] 1639 patients were randomised to aliskiren or placebo around 5 days after an index heart failure admission, again in addition to standard therapy. There was no effect on the main outcome measures of cardiovascular death or rehospitalisation with heart failure at 6 and 12 months, but a definite signal that aliskiren might be deleterious in patients with diabetes.

The ATMOSPHERE study[31] is rather different. It is a study of patients with chronic heart failure due to left ventricular systolic dysfunction and a raised natriuretic peptide level. Patients are randomised to aliskiren, enalapril or both. Fewer patients have diabetes (around a third), and renal function is considerably less impaired in patients in the ATMOSPHERE trial than in those in the ALTITUDE study.[32] The results of the ATMOSPHERE trial should give a much more profound understanding of the possible role of aliskiren: it is surely possible that it might have a role as an alternative to conventional RAAS blockade rather than as an add-on.

Aldosterone antagonists

The problem of heart failure with a normal ejection fraction (HeFNEF) remains tricky. It has proved a difficult entity to define clinically despite its apparent frequency in epidemiological studies, and no clinical trial has yet shown any convincing benefit from any treatment strategy. Another disappointment is spironolactone. In patients with heart failure due to left ventricular systolic dysfunction, there is no doubt that mineralocorticoid antagonists help improve cardiac function, symptoms and survival.[33] Mineralocorticoid antagonists
might be thought to be particularly likely to work in HeFNEF through their antifibrotic properties. However, in the Aldo-DHF study conducted in 422 patients with HeFNEF, spironolactone had no effect on exercise capacity, symptoms or quality of life.[34] The mean N-terminal prohormone of brain natriuretic peptide level in the patients included in the study was only 158 ng/L, suggesting that yet again a trial of HeFNEF has included patients who really do not have heart failure or, if they do, they are patients with an intrinsically good prognosis.

Device Therapy and Monitoring

Remote monitoring

There has been a great deal of enthusiasm for telemonitoring, particularly among commissioners who see it as a way of reducing admissions to hospital among patients with chronic disease. The role of remote monitoring for patients with heart failure has been much debated. Although early studies suggested that there might be a major benefit, more recent trials have been much less positive, perhaps because the background standard of care against which telemonitoring is being compared has improved.

It might be that targeted intensive monitoring during periods of high risk, such as immediately after hospital discharge, makes the best use of remote monitoring. In a meta-analysis of trials involving over 6000 patients, Pandor et al[35] found that remote monitoring following an admission with heart failure was associated with improved survival, particularly where usual care was less good.

Defibrillators

It is commonly thought that having discharges from an implantable cardioverter-defibrillator (ICD), whether

appropriate or inappropriate, is associated with an adverse prognosis in patients with heart failure.[36] The commonest reason for an inappropriate shock is atrial fibrillation with a rapid ventricular response; additionally, it is becoming increasingly apparent that antitachycardia pacing may treat ventricular tachycardia without a shock being necessary. The MADIT-RIT trial[37] reported that programming techniques that both increase antitachycardia pacing and delay ICD discharges reduce the risk of inappropriate discharge. There was a reduction in all-cause mortality of around a half in the advanced programming group.

Intriguingly, in a cohort study of 1698 patients, Deyell et al[38] found no association between inappropriate ICD shock and an adverse outcome. In contrast, an appropriate shock was associated with a HR of 3.11 for the combined endpoint of death and transplantation. The reasons for the discrepancy are not clear: it may be related to the fact that the patients in Deyell et al's cohort were less severely symptomatic and were more likely to be on β blocker therapy. However, regardless of the prognostic implications, by reducing inappropriate shocks, advanced programming of ICDs improves patients' quality of life by reducing the risk of a very unpleasant ICD discharge.

Cardiac resynchronisation therapy

The other major device for heart failure is, of course, the cardiac synchronisation therapy (CRT) pacemaker. Although it has been proved to increase life expectancy in patients with heart failure due to left ventricular systolic dysfunction, sinus rhythm and left bundle branch block, controversies remain. Many are convinced that patients in atrial fibrillation or other forms of conduction defect might benefit, although there is no evidence from randomised trials to support these beliefs.[39 40] A particular recurring theme is the concept of 'response': around a third of patients are said not to respond to CRT based on either their symptom status or some echocardiographic index of left ventricular function. The subtext is that there might be some patients with conventional indications for CRT who perhaps should be denied the treatment, and others with no indication who might benefit based on some measure of so-called dyssynchrony preoperatively.

As Witte points out,[41] deactivating a CRT device in a supposed 'non-responder' results in haemodynamic worsening.[42] Defining 'response' in terms of symptomatic change, or worse, a surrogate measure such as left ventricular volume, is doomed to fail—we cannot know what would otherwise have happened to the patient without the device. One interesting new piece of information is that there appears to be an inverse relation between the duration of heart failure symptoms prior to CRT implantation and subsequent survival, particularly in those with abnormal renal function.[43] This finding is surely expected: the earlier in the natural history of illness we intervene, the greater is the likely effect. However, it does highlight the need to think about implanting CRT in patients with less severe symptoms if they have left bundle branch block,[44] rather than waiting until patients are worse but may have less to gain.

Further encouragement for earlier CRT implantation comes from the BLOCK-HF study in which patients with impaired left ventricular systolic function and a conventional indication for pacing in the shape of atrioventricular block were studied.[45] All the patients had a CRT device implanted, but they were randomised later to conventional dual chamber pacing or biventricular pacing. Nearly 700 patients were included, and the average left ventricular ejection fraction was as high as 40%. None had a conventional indication for CRT. Those receiving active CRT pacing had a reduction in the primary endpoint of all-cause mortality, heart failure-related urgent care or a >15% increase in left ventricular end-systolic volume.

Vagal stimulation

A fascinating new device for patients with chronic heart failure is the vagal stimulator, which might potentially be combined with existing devices.[46] Patients with chronic heart failure commonly have an imbalance between their enhanced sympathetic nervous system activity and a decline in parasympathetic activity. The vagal stimulator delivers electrical stimulation to the vagus nerve in the neck, timed to the cardiac cycle. Preliminary work suggested that it might have some effect on exercise capacity and quality of life and left ventricular function.[47] A study of 650 patients is being mounted to assess its effects on all-cause mortality and hospitalisation for heart failure.[48]

End-Stage Heart Failure

For patients with end-stage heart failure, there has been some controversy as to whether implantable defibrillators should be used. The UK guidelines on referral for heart transplantation[49] address the issue of use of implantable defibrillators in terms of NICE guidance, and point out that we do not have much information to guide the management of those without ischaemic heart disease. However, patients on cardiac transplant waiting lists are at high risk of sudden death, and in a retrospective observational study of over 1000 patients listed for potential cardiac transplantation, Frölich et al found a marked survival benefit for patients receiving an ICD for primary prevention independent of the aetiology of heart failure—only around one-third of the patients had ischaemic heart disease.[50] The effect was very much less marked for patients receiving an ICD for secondary prevention. Maybe ICDs should be considered more widely in patients on a transplant waiting list.

Some cells from myocardial biopsy samples cluster together to form cardiospheres which can potentially differentiate into many cell types. In a very small study to demonstrate safety, patients treated with intracoronary cardiosphere-derived cells (CDCs) following myocardial infarction had smaller volumes of scar and larger volumes of viable heart mass than those receiving standard care.[51] CDCs join a long list of potential sources of stem cells, none of which has really borne fruit despite enormous enthusiasm.

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Almanah 2013

Almanah 2013: novel non-coronary cardiac interventions

The national society journals present selected research that has driven recent advances in clinical cardiology. The article was first published in Heart 2013;99:18 1309-1316 Published Online First: 30 July 2013 doi:10.1136/heartjnl-2013-304430, and is republished with permission.

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Abstract 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.

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 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), non-pharmacologic 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.

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

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'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 specific- ally 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 complications 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 contra- indications 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:
– Percutaneous LAA closure is a promising alternative to war farin 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.[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 mitral leaflet is held between the arms and each side of the U-shaped gripper. Then, the clip is closed and locked so that the two leaflets 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 leaflet 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 leaflets 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 con- ventional 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.

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 con- currently 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%; $p < 0.0001$), 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 prerandomisation 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 im-

provement is comparable. The most suitable patients are those 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, pre- dominantly 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]

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 post- operative 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 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 post- procedural 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 con- founding 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 2000 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, Minnesota, USA). It has porcine pericardial leaflets 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 com- paring 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' indica- tions 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 post- procedural 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.

The TriGuard Cerebral Protection Device (Keystone Heart, Israel, formerly SMT R&D) works as a debris deflector instead of a debris collector. A similar device is the Embrella Embolic Deflector (Edwards Lifesciences, Irvine, California, USA). Both Embrella and TriGuard have a protective shield that deflects 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 deflector 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 mm Hg or >130–139/80–85 mm Hg in diabetic patients, or >130/80 mm Hg 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 ≥160 mm Hg 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.

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 study 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 mm Hg) was sustained at 12 months (−28 mm Hg). At 6 months, the control group had shown an increase in blood pressure from 182.8±16.3 to 190.0 ±19.6 mm Hg. 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 (−24 mm Hg; $p<0.001$ for difference from before the procedure). This sub- stantiated 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 5000 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-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 mm Hg; 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 mm Hg reduction in mean blood pressure). The mean reduction in blood pressure at 12 months was 27 mm Hg. 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 invasive 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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Almanah 2013

Almanac 2013: stable coronary artery disease

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Coronary Heart Disease In Decline

Epidemiological data from Europe, the USA and elsewhere in the developed world show a steep decline in coronary heart disease (CHD) mortality during the last 40 years.[1] Concern about levelling of mortality rates in younger adults[2] has been somewhat alleviated by data from The Netherlands showing that in men aged <55 years, rates of decline have again accelerated, increasing from only 16% in 1993–1999 to 46% in 1999–2007.[3] A similar pattern was observed in young women with rates of decline of 5% and 38% during the same time periods. This is encouraging, particularly in the context of data from Denmark and the UK showing declining mortality and also a sharp fall in standardised incidence rates for acute myocardial infarction indicating that coronary prevention, as well as acute treatments, has contributed to recent mortality trends.[4 5] Meanwhile an Australian study reminds us that myocardial infarction is but one of several manifestations of cardiovascular disease by reporting that decreasing incidence and recurrence rates for hospitalised CHD from 2000 to 2007 have also been seen for cerebrovascular and peripheral arterial disease.[6]

However, the epidemiological news is not all good, and data from the UK show that the pernicious relationship between socioeconomic status (SES) and CHD has shown no tendency to go away in recent years, the gradients between top and bottom SES quintile groups for hospital admissions remaining essentially unchanged across the age range.[7] Whether this has contributed to the almost 3-fold risk of myocardial infarction associated with stillbirth and 9-fold risk associated with recurrent miscarriage in a recent German study is unclear because the investigators made no adjustment for SES.[8] Nor is it clear if SES has contributed to the persistent ethnic differences in both US and UK studies of CHD mortality although other factors appear also to be important. Thus, African–American men have greater exposure to CHD risk factors than Caucasians and, when adjustment is made for this, their susceptibility to CHD is no greater, although mortality rates are twice as high.[9] For African–American women, incidence and mortality rates are higher than their Caucasian counterparts. These findings suggesting that exposure to risk factors contributes to ethnic differences in the incidence of CHD are to some extent reflected in a recent report from the Health Survey for England in which 13 293 Caucasian and 2120 S Asians consented to mortality follow-up.[10] Physical inactivity increased susceptibility to disease and not by increased case-fatality rates.[11]

Diagnosis Of Stable Coronary Artery Disease

The recent AHA/ACC guideline update[12] emphasised the importance of individualising the diagnostic workup based on the estimated probability of coronary artery disease. In this respect, it mirrored an earlier National Institute of Clinical Excellence (NICE) guideline on chest pain diagnosis,[13] but there were important differences in the recommendations for non-invasive testing, the new AHA/ ACC guideline preferring the exercise ECG as the initial diagnostic approach for most patients, (NICE had previously counselled against use of the exercise ECG based on its relatively poor diagnostic performance) with pharmacologic radionuclide, cardiac MRI or stress echocardiography testing in reserve for patients unable to exercise. Recommendations for cardiac CT coronary angiography (CTCA) were cautious, and invasive angiography was recommended for diagnostic purposes only if the results of non-invasive testing suggested a high likelihood of severe 3-vessel or left main coronary artery disease, and the patient was willing to undergo revascularisation. In general, therefore, the AHA/ACC guideline update was less prescriptive than the earlier NICE guideline, perhaps partly because it put less emphasis on the cost effectiveness of its recommendations.

Management of Stable Coronary Artery Disease

The recent NICE guideline[14] recommended initial treatment with a short-acting nitrate and a β-blocker and/or a calcium channel blocker for control of angina plus aspirin and a statin for secondary prevention. Lifestyle measures were also emphasised. For patients with con-

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tinuing symptoms cardiac catheterisation with a view to revascularisation was recommended, additional anti-anginal treatment (long-acting nitrates or one of the newer agents) only being indicated for patients unsuitable for revascularisation. It was further recommended that the mode of revascularisation (percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG)) should best be determined by a multidisciplinary group, a recommendation that has also been emphasised by European guideline groups,[15] bearing in mind the potential for prognostic benefit from CABG in patients with complex multivessel and left main stem disease,[16] was more frequent in S Asians compared with particularly those with diabetes.

For patients with Caucasians (47% vs 28%) and explained >20% of their excess CHD mortality. Certainly, the emerging consensus is that the excess CHD mortality among UK S Asians is driven almost entirely by their symptoms adequately controlled with medical treatment, the guideline recommended discussion of the potential for prognostic improvement with CABG. Those patients prepared to proceed to CABG might then be offered diagnostic cardiac catheterisation to rule out complex multivessel and left main stem disease, which a recent meta-analysis reported in as many as 36% (18.5–48.8%) of cases of stable coronary disease selected for cardiac catheterisation.[17]

Secondary Prevention of Stable Coronary Disease

The scope for improving secondary prevention in patients with stable coronary artery disease has been emphasised in two recent reports. In The multinational REduction of Atherothrombosis for Continued Health (REACH) Registry, 20 588 symptomatic patients were analysed for 'good control' of cardiovascular risk factors, defined as three to five of systolic blood pressure <140 mm Hg, diastolic blood pressure <90 mm Hg, fasting glycaemia <110 mg/dL, total cholesterol <200 mg/dL, non-smoking.[18] Only 59.4% had good control of risk factors at baseline, but this was associated with lower mortality (OR 0.89; 95% CI 0.79 to 0.99) at 36 months, compared with poor control. In the UK ASPIRE-2-PREVENT survey, 676 patients with CHD (25.6% women) had the following rates of major risk factors: smoking 14.1%, obesity 38%, physical inactivity 83.3%, blood pressure ≥130/80 mmHg, total cholesterol ≥4 mmol/L and diabetes 17.8%, leading the authors to conclude that there is considerable potential for reducing cardiovascular risk in these patients and thereby improve prognosis.[19]

Clopidogrel. The availability of low-cost generic clopidogrel prompted a NICE review of its cost effectiveness which recommended it should now supersede aspirin in certain high-risk groups, namely patients with multivascular disease, peripheral vascular disease and myocardial infarction.[20] However, clopidogrel is metabolised by enzymes in the hepatic cytochrome P450 (CYP) system, and variability in its antiplatelet activity may occur because the activity of these enzymes is influenced by common genetic variations, and also by a number of commonly used drugs. Several studies have reported loss-of-function alleles in CYP2C19 that result in reduced activation of clopidogrel[21] and a modest lowering of antiplatelet activity[22] which have been associated with an increased risk of cardiovascular events in some meta-analyses.[23] Conversely, gain-of-function alleles have been associated with reduced cardiovascular risk among clopidogrel-treated patients[24] A recent meta-analysis, however, has commented on the tendency of small studies to bias conclusions about the way genetic variants influence clinical outcomes, and in larger studies of clopidogrel therapy with ≥200 outcome events found no effect of loss-of-function alleles on cardiovascular risk.[25] At present, therefore, there seems to be no compelling indication for genetic testing to guide clopidogrel treatment although the topic remains a subject of ongoing debate. Also debated is the interaction of clopidogrel with some commonly used drugs, particularly proton pump inhibitors (PPI) and amlodipine. A recent meta-analysis of studies of PPIs in patients treated with clopidogrel found clear evidence of reduced platelet activity but although clinical outcomes appeared adversely affected by the interaction, the authors urged cautious interpretation, pointing out the heterogeneity caused by retrospective studies. When analysis was restricted to prospective studies of PPIs and clopidogrel, adverse clinical consequences could no longer be demonstrated (OR 1.13 (0.98 to 1.30)).[26] Similarly, the clinical impact of amlodipine on responsiveness to clopidogrel remains uncertain. Certainly, there is evidence of interaction, and in one study of 1258 patients receiving clopidogrel, amlodipine administration was associated with higher on-treatment platelet reactivity only in those patients with a loss-of-function P450 (CYP) genotype (249±83 vs 228±84 P2Y12 reaction units), and this was associated with a higher incidence of cardiovascular events (4.6% vs 0.6%).[27] However, in a more recent randomised trial, platelet function in 98 patients with stable coronary artery disease taking clopidogrel was similar regardless of amlodipine therapy.[28] At present, therefore, there is no guideline recommendation about concomitant prescription of these drugs in patients taking clopidogrel.

Statins, Niacin and cholesteryl ester transfer protein (CETP) inhibitors. The benefits of statins for secondary prevention in patients with stable coronary artery disease are well established. Cardiovascular endpoints are reduced in proportion to the degree of LDL-cholesterol reduction, probably in response to stabilisation and regression of atheromatous plaque. The capacity for plaque regression has recently been confirmed by serial IVUS examination in 1039 patients with stable coronary disease randomised to rosuvastatin 40 mg daily or atorvastatin 80 mg daily.[29] Atheroma volume during the 2-year monitoring period decreased by an average of about 1% in both groups, more than previously reported with less intensive statin regimens. However, additional clinical benefits of niacin have now been unequivocally ruled out in the AIM-HIGH trial in which 3414 patients with stable cardiovascular disease taking statins were randomised to receive niacin (n=1718) or placebo (n=1696).[30] Although

niacin significantly increased HDL cholesterol and lowered triglycerides, differences in the primary endpoints (a composite of adverse coronary events, strokes and revascularisation) were negligible, occurring in 16% of patients in each group. The trial was stopped after an average follow-up of 3 years when it became clear HDL raising therapy with niacin was clinically ineffective. All hopes for HDL raising therapy are now invested in CETP inhibitors, and despite safety concerns following the ILLUMINATE trial of torcetrapib,[31] in which treatment was associated with increased mortality despite substantial HDL elevations, other CETP inhibitors are now entering phase III trials. A recent randomised trial of dalcetrapib in patients with acute coronary syndromes was disappointing with no reduction in the risk of recurrent coronary events despite a >30% increase in HDL levels in the treatment group.[32] An efficacy and safety trial of anacetrapib in patients with, or at high risk of, stable coronary disease was favourable, although not powered for clinical outcomes,[33] and evacetrapib has now entered the arena with a recent study showing effective HDL raising without the adverse effects on blood pressure seen with torcetrapib and, to a lesser extent, dalcetrapib.[34] Whether any of these CETP inhibitors will improve clinical outcomes, however, remains unknown.

Novel lipid-lowering drugs in clinical translation. Conventional lipid-lowering therapies, even when combined with LDL-apherisis, are often insufficient to treat to guideline targets patients with familial hypercholesterolaemia (FH), an autosomal dominant disorder of lipid metabolism associated with accelerated coronary disease.[35] There is, therefore, considerable interest in novel therapies currently under investigation, particularly lomitapide, an oral inhibitor of microsomal transfer protein and monoclonal antibodies against PCSK9. A phase II study of lomitapide in homozygous FH showed a 50% reduction in LDL-cholesterol and, although gastrointestinal side effects were common, a useful role for the drug seems likely in these homozygous patients.[36] PCSK9 inhibitors have also produced 50–60% reductions in LDL-cholesterol values in clinical studies when added to statins and ezetimibe, but unlike lomitapide, are probably mainly effective in heterozygotic FH because they act through interference with LDL receptors which are dysfunctional or completely absent in homozygotes.[37 38] The expectation is that application of these new drugs will allow most patients with FH to achieve target concentrations of LDL cholesterol. An important component of FH management involves identification of other affected family members, and cascade screening using genetic testing has been reported as cost effective.[39] However, recent evidence suggests that polygenic disorders account for an appreciable proportion of FH cases,[40] and this will limit the effectiveness of cascade screening to relatives of mutation-positive (monogenic) cases. In other patients, with cholesterol levels consistent with an FH genotype, more conventional primary care strategies[41] should remain the screening tool of choice, at least for the time being.

Revascularisation in Stable Cad

Percutaneous coronary intervention. The COURAGE trial was a game-changer, showing that coronary stenting in patients with stable angina did not improve cardiovascular outcomes compared with optimal medical therapy (OMT) while quality-of-life benefits were short-lived.[42 43] Now available is a meta-analysis comparing contemporary medical therapy and PCI in eight randomised trials involving 7229 patients with stable CAD.[44] Again, cardiovascular outcomes between the groups were similar during follow-up for an average 4.3 years with no significant clinical benefit for PCI, risks of death (8.9% vs 9.1%) and non-fatal MI (8.9% vs 8.1%) being nearly identical with medical therapy, while differences in unplanned revascularisation (21.4% vs 30.7%) and persistent angina (29% vs 33%) were small and insignificant. The data support recent guideline recommendations for treatment of stable angina (see above), and have been used to challenge those clinicians who continue to offer PCI to patients not receiving OMT.[45] However, FAME-II has now provided some support for an early interventional approach in a randomised comparison of OMT and PCI using drug-eluting stents guided by fractional flow reserve (FFR).[46] The study was stopped 17 months earlier than planned because the composite endpoint (all-cause mortality, non-fatal MI, urgent revascularisation) occurred in 4.3% of the PCI group compared with 12.7% of the non-PCI (OMT) group. Relief of angina was also more effective in the PCI group. Already, PCI guided by FFR has become a recommended strategy in stable coronary artery disease but some feel this is premature.[47] Thus, the treatment difference in FAME-II was driven solely by a reduction in urgent revascularisation (49 in the OMT alone group; 7 in the FFR-PCI group (HR=0.13, 95% CI 0.06 to 0.30), while the 33 deaths and non-fatal MIs were distributed fairly evenly between the groups. Moreover, the majority of patients undergoing 'urgent' revascularisation lacked objective findings of high-risk ischaemia or threshold biomarker elevations, raising concerns of biased selection of patients for invasive management during follow-up. Nevertheless, the argument in favour of interventional management as an initial strategy in stable angina has undoubtedly been strengthened by FAME-II, but final answers to the debate may have to await the findings of the ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA Trial; ClinicalTrials.gov number, NCT 01471522), comparing effects of revascularisation (PCI or CABG) combined with OMT, with OMT alone on cardiovascular death, or MI in patients with stable CAD, and objective evidence of myocardial ischaemia.

Coronary artery bypass surgery. Updated US guidelines[48] have endorsed the NICE recommendation of a multidisciplinary team approach to adjudicating revascularisation decisions in patients with complex coronary disease, encouraging application of SYNTAX and other scoring systems in arriving at an appropriate decision.[49] The potential for CABG compared with PCI to improve prognosis in patients with left main and multivessel CAD is supported

by recent cohort studies,[50 51] and now available are the 5-year follow-up data from SYNTAX in which major adverse cardiac and cerebrovascular events (MACCE) were 26·9% in the CABG group and 37·3% in the PCI group, driven largely by lower rates of non-fatal myocardial infarction and repeat revascularisation for CABG, with no significant difference in all-cause mortality and stroke compared with PCI.[52] The benefits of CABG were particularly evident in patients with intermediate and high SYNTAX scores, there being no significant difference in outcomes between revascularisation strategies for patients with low SYNTAX scores. Any question about the preferred revascularisation strategy in patients with diabetes and mutlivessel coronary artery disease has now been answered by the FREEDOM TRIAL which randomised 1900 patients on OMT to either PCI with drug-eluting stents or CABG.[53] After a median follow-up of 3.8 years, the primary outcome, a composite of death from any cause, non-fatal myocardial infarction, or non-fatal stroke, occurred in 26.6% of the PCI group and 18.7% of the CABG group. The authors concluded that CABG is superior to PCI in patients with diabetes and multivessel disease. There is less certainty about the preferred revascularisation strategy in left main coronary disease, the SYNTAX investigators reporting similar outcomes for PCI and CABG, a finding consistent with other contemporary studies that identify stenting as a reasonable strategy in appropriately selected cases, even though the need for repeat revascularisation is almost invariably higher compared with CABG.[54 55]

Surgical technique has come under considerable scrutiny recently. Concerns about the potential adverse effects of endoscopic versus open saphenous vein harvesting have been based largely on a non-randomised cohort study of 1817 patients in whom rates of vein graft failure at 1 year were 47% vs 38%, and rates of death, myocardial infarction or revascularisation at 3 years were 20.2% vs 17.4% for endoscopic versus open saphenous vein harvesting.[56] This led NICE to recommend caution in use of the endoscopic technique,[57] but such concerns have now been allayed by the results of two large cohort studies. In the US study of 235 394 Medicare CABG patients in the Society of Thoracic Surgeons (STS), national database mortality rates were similar regardless of harvesting technique, while rates of harvest site complications were lower for the endoscopic technique.[58] A UK study of 4702 CABG patients reported similar findings with no differences in in-hospital mortality (0.9% vs 1.1%, p=0.71) or midterm mortality (HR 1.04; 95% CI 0.65 to 1.66) for endoscopic versus open vein harvesting.[59]

Also under scrutiny have been the relative benefits of off-pump and on-pump CABG. Each has its proponents,[60 61] but the results of randomised outcome trials have failed to show any clear advantage for off-pump CABG, the 3-year results of the Best Bypass Surgery Trial showing no significant difference in the primary composite outcome of MACCE compared with on-pump CABG, but a tendency towards higher mortality.[62] This may reflect, at least in part, differences in graft patency rates favouring on-pump procedures, the ROOBY trial reporting rates of 91.4% vs 85.8% for arterial grafts and 80.4% vs 72.7% for saphenous vein grafts in on-pump compared with off-pump patients.[63] Particularly disappointing has been the failure of off-pump surgery to reduce cerebral injury, but a randomised comparison of minimal (MECC) versus conventional (CECC) extracorporeal circulation in 64 patients undergoing CABG has been more promising.[64] MECC was associated with improved cerebral oxygen delivery during surgery, and neurocognitive performance at 3 months was better when compared with CECC.

Remote Ischaemic Preconditioning for Treatment of Stable Coronary Disease

Its proponents see remote ischaemic preconditioning (RIPC) as a useful and inexpensive means of improving outcomes across a range of cardiovascular disorders. They must be frustrated, therefore, by the technique's failure to penetrate clinical practice, conflicting reports of its efficacy and mechanistic uncertainty combining to undermine clinical confidence in the utility of RIPC. Some recent randomised trials have been favourable, reporting protection against contrast-induced nephropathy during cardiac catheterisation[65] and reduction in myocardial injury during heart valve surgery.[66] Perhaps the most favourable has been a randomised trial of prehospital RIPC in 333 patients with STEMI who underwent primary PCI.[67] The group with RIPC showed a significant improvement in myocardial salvage index compared with the group without (0.75 vs 0.55) although the trial was not powered for coronary events. Against this must be set a negative trial of RIPC in a group of patients undergoing CABG,[68] but this is unlikely to be the last word, and already a meta-analysis of nine studies including 704 patients has concluded that RIPC significantly reduces troponin release during CABG.[69] Mechanistic studies of interest include one crossover study in patients with stable coronary artery disease in which RIPC reduced platelet activation during exercise testing without protecting against ischaemic ECG changes.[70] In another study of forearm blood flow using venous plethysmography in healthy volunteers, RIPC protected against impaired endotheliumdependent vasomotor function induced by ischaemia.[71] However, this protection was unaffected by infusion of a bradykinin B2 receptor antagonist, leading the authors to conclude that bradykinin is not a mediator of RIPC.

Prognostic Biomarkers in Stable Cad

Circulating biomarkers. Interest in circulating cardiovascular biomarkers has never been higher, and methodological papers have been developed to alert researchers to the standards necessary for proper evaluation of their prognostic utility.[72 73] However, a systematic review of 83 CRP studies was critical of their general quality and concluded that 'multiple types of reporting bias, and publication bias, make the magnitude of any independent association between CRP and prognosis among patients with stable coronary disease sufficiently uncertain that no clinical practice recommendations can be made'.[74] The same authors were

equally critical of 19 BNP studies in patients with stable coronary disease, reporting that clinically useful measures of prediction and discrimination were generally unavailable, and concluding that the unbiased strength of association of BNP with prognosis in stable coronary disease is unclear.[75] The availability of highsensitivity assays has seen renewed interest in troponins as markers of risk in stable coronary disease, a US study of 984 patients in the Heart and Soul Study reporting that each doubling in hs-cTnT level is associated with a 37% higher rate of cardiovascular events.[76] Meanwhile the PEACE investigators have reported that among 3623 patients with stable coronary artery disease, hs-cTNI is independently associated with cardiovascular death or heart failure (HR 1.88 (1.33 to 2.66; p<0.001)), the association with non-fatal myocardial infarction being weaker (1.03 to 2.01; p=0.031).[77] Evidence from CTCA suggests that clinically silent rupture of non-calcified plaque with subsequent microembolisation is a likely pathophysiological mechanism of troponin elevation[78] but it is too soon to know whether it will have a clinical role in the prognostic assessment of stable coronary artery disease. The same applies to the mid-regional portion of pro-adrenomedullin and other biomarkers currently under investigation.[79]

Vascular biomarkers. Carotid intimamedia thickness (cIMT) is well established as a predictor of cardiovascular events in the general population and, more weakly, in patients with stable coronary artery disease.[80] Its predictive value may be enhanced by additional consideration of the extent of carotid plaque allowing derivation of the 'total burden score' which was shown by Chinese investigators to improve the prediction of the 5-year risk of cardiovascular endpoints compared with cIMT alone.[81] Certainly, the value of cIMT alone for cardiovascular risk prediction in the general population is under question following a large meta-analysis of participant-level data in 45 828 individuals in which cIMT added almost nothing to the Framingham Risk Score.[82] Further questions have been raised by another meta-analysis of participant-level data which included 36 984 individuals followed-up for an average of 7 years.[83] The investigators showed no association between progression of cIMT and risk of cardiovascular events, questioning the validity of using changes in cIMT as a surrogate endpoint in trials of cardiovascular risk.

Calcium and parathyroid hormone. Studies suggesting that people who take calcium supplements may be increasing their risk of myocardial infarction[84 85] have stimulated interest in serum calcium and its relation to cardiovascular events in patients with CHD. A recent study has confirmed that vitamin D, parathyroid hormone and calcium show association with cardiovascular risk factors in US adolescents,[86] and now we have data in 1017 patients with stable coronary artery disease followed-up for a median of 8.1 years, suggesting that high calcium levels, but not high phosphate levels, might be associated with all-cause and cardiovascular mortality (HR 2.39 to 4.66)).[87] The mechanism of this association is unclear, but the demonstration in the same cohort of a similar association between high parathyroid hormone and cardiovascular mortality may implicate calcium mobilisation from bone on the causal pathway.[88]

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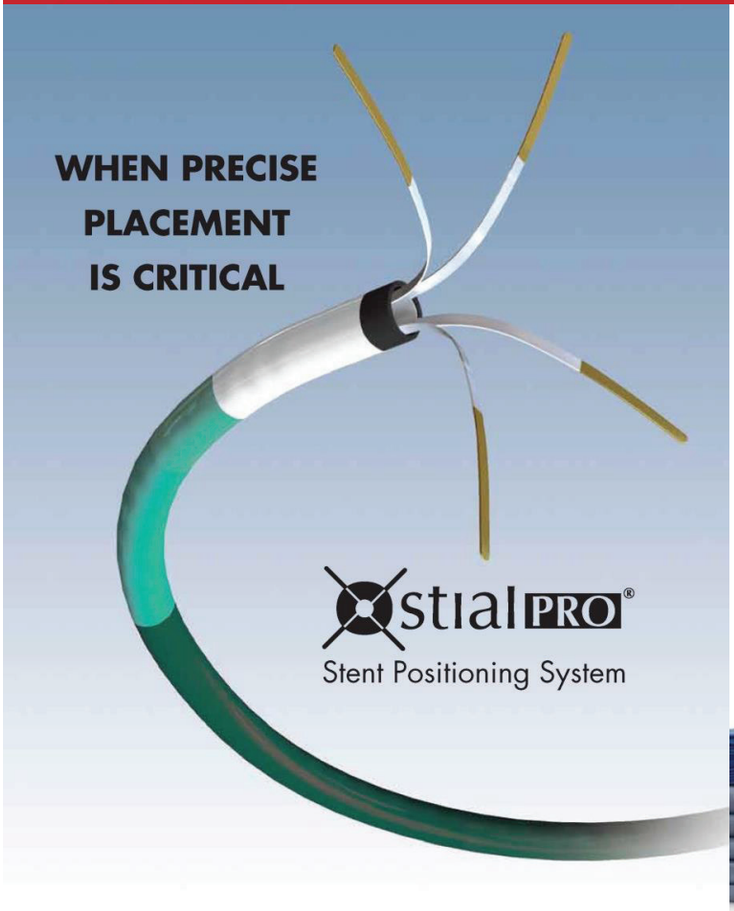

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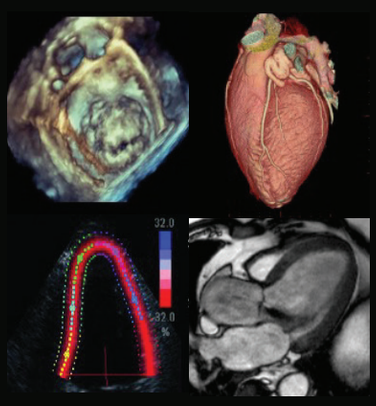

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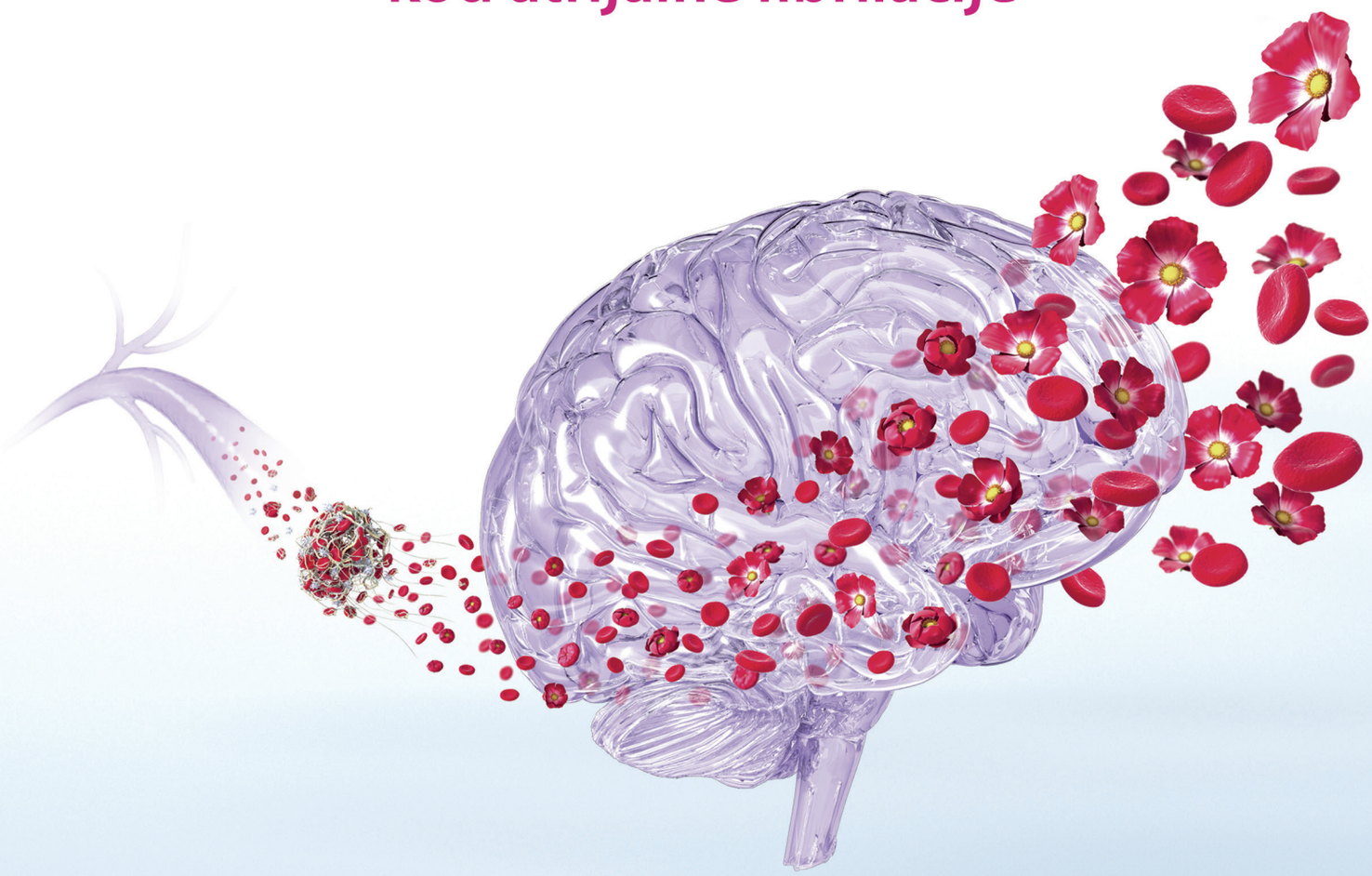

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