Pregledni članak / Review article

Almanah 2012.: intervencijska kardiologija. Časopisi nacionalnih društava predstavljaju odabrana istraživanja koja donose napredak u kliničkoj kardiologiji

Almanac 2012: interventional cardiology. The national society journals present selected research that has driven recent advances in clinical cardiology

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SAŽETAK: Područje intervencijske kardiologije nastavlja se brzo razvijati. Učinkovitost perkutanih intervencija primjenom nove generacije stentova koji izlučuju lijekove znatno se povećala u zadnjih deset godina. Takvo poboljšanje učinkovitosti stentova proširilo je i indikacije na sve složenije intervencije poput perkutane koronarne intervencije (PCI) na glavnom stablu lijeve koronarne arterije ili intervencija na više koronarnih arterija. Najveći napredak i dalje je na području farmakološkog liječenja, kao npr. antitrombocitne terapije (bivalirudin, prasugrel, tikagrelor), što će još više poboljšati ishode PCI. Isto vrijedi i za slikovni prikaz uporabom intravaskularnog ultrazvuka i optičkom koherentnom tomografijom. Međutim, intervencijska kardiologija obuhvaća široko područje, koje uključuje i alkoholnu septalnu ablaciju kod hipertrofijske opstruktivne kardiomiopatije i slične postupke. Trenutno se najbrže razvija područje strukturalnih intervencija, osobito kod stenoze aortnog zaliska (transkateterska implantacija aortnog zaliska) i mitralne regurgitacije ("mitral clipping").

Ovaj pregledni članak prikazuje nova dostignuća na različitim područjima intervencijske kardiologije.

SUMMARY: The field of interventional cardiology continues to progress quickly. The efficacy of percutaneous interventions with newer generation drug-eluting stents has advanced a lot over the last decade. This improvement in stent performance has broadened the level of indication towards more complex interventions such as left main and multivessel PCI. Major improvements continue in the field of medical co-therapy such as antiplatelet therapies (bivalirudin, prasugrel, ticagrelor) and this will further improve outcomes of PCI. The same is true for intravascular imaging such as ultrasound IVUS and optical coherence tomography OCT. However, interventional cardiology has become a rather broad field, also including alcohol septal ablation for hypertrophic obstructive cardiomyopathy, etc. At the moment, the fastest growing area is the structural interventions, especially for aortic valve stenosis (transcatheter aortic valve implantation TAVI) and for mitral regurgitation (mitral clipping).

This review covers recent advances in all these different fields of interventional cardiology.

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Perkutana koronarna intervencija naspram farmakološkog liječenja

Za liječenje infarkta miokarda (MI) s elevacijom ST-segmenta, kao i MI bez elevacije ST-segmenta preporučena terapija prema smjernicama je perkutana koronarna intervencija (PCI).[1] Međutim, uloga PCI kod stabilne koronarne bolesti srca (KBS) se preispituje nakon rezultata studije COURAGE, prema kojima PCI nije poboljšala kardiovaskularne ishode kod bolesnika na optimalnoj farmakološkoj terapiji, dok se unutar 36 mjeseci postupno smanjivala dobrobit na kvalitetu života.[2,3] Novija meta-analiza koja je obuhvatila osam istraživanja i 7.229 bolesnika uspoređivala je optimalnu farmakološku terapiju naspram PCI potkrijepila je zaključke COURAGE studije pokazavši da ne postoje značajne razlike što se tiče smrtnosti (9,1% naspram 8,9%), nefatalnog MI (8,1% naspram 8,9%), neplanirane revaskularizacije (30,7% naspram 21,4%) i perzistentne angine pektoris (33% naspram 29%).[4] Stentovi koji izlučuju lijekove (DES) korišteni su samo kod malog broja tih bolesnika te je moguće da su smanjili potrebu za daljnjom revaskularizacijom i poboljšali simptomatske odgovore. Ipak, meta-analiza potvrđuje suvremene smjernice koje preporučuju optimalnu terapiju lijekovima kao prvu terapiju kod stabilne angine pektoris.[5] Hoće li to promijeniti sadašnju praksu ostaje nejasno, no rani znakovi za to nisu ohrabrujući. Analiza bolesnika iz američkog registra bolesnika koji su liječeni primjenom PCI prije (N = 173.416) i nakon (N = 293.795) COURAGE studije nije pokazala nikakve promjene onih koji su podvrgnuti optimalnoj farmakološkoj terapiji (43,5% naspram 44,7%).[6]

PCI naspram aortokoronarnog premoštenja

Dva su nedavna istraživanja potvrdila sigurnost PCI u bolnicama bez kardiokirurške službe.[7,8] Kako se PCI može primijeniti sve više kod složene bolesti, ne treba dalje objašnjavati zašto se u posljednjih nekoliko godina broj operacija aortokoronarnih premoštenja (CABG) znatno smanjio. Prema nedavnom američkom istraživanju o postupcima revaskularizacije provedenima od 2001. do 2008. godine, broj CABG se smanjio za 38%, dok se broj PCI smanjio za samo 4%.[9] Neki se pitaju savjetuju li se bolesnici na odgovarajući način i u skladu sa suvremenim smjernicama,[10] jer prema jednom američkom istraživanju koje je obuhvatilo 500.154 PCI, od 28,9% zahvata provedenih kod neakutnih indikacija samo 50,4% zahvata je bilo primjereno, dok kod mnogih neprimjerenih zahvata bolesnici nisu imali anginozne tegobe.[11] U nedostatku dokaza o boljoj prognozi, trenutno nema indikacije za PCI kod stabilnih bolesnika koji nemaju anginozne tegobe. Prema rezultatima novijeg istraživanja koje se temeljilo na studiji SYNTAX kod bolesnika s anginom pektoris, PCI je jednako učinkovit kao CABG u ublažavanju simptoma tijekom praćenja od 12 mjeseci.[12] Međutim, prednost CABG je što donosi prognostičku dobrobit, a prema novijim podacima iz američkog registra, učestalost smrtnosti u razdoblju od četiri godine je manja nego kod PCI (16,4% naspram 20,8%).[13] Obzirom da se radi o istraživanju koje se temelji na podacima iz registra, distribucija terapijskog postupka nije bila randomizirana, pa stoga treba s oprezom donositi zaključke vezane za prognozu. Ipak, smjernice preporučuju kardiokirurški zahvat kod trožilne KBS i bolesti glavnog stabla lijeve koronarne arterije, iako mnogi bolesnici i dalje radije odabiru liječenje primjenom PCI, osobito sada kada postoje rezultati o primjenjivosti i sigurnosti te otpustu iz bolnice istoga dana. To se osobito odnosi na radijalni pristup (ili ugradnju sistema za zatvaranje femoralne arterije nakon zahvata), jer prema istraživanju provedenom na podacima iz američkog registra, kod 1.339 bolesnika koji su

Percutaneous coronary intervention versus medical treatment

Percutaneous coronary intervention (PCI) has guideline recommendations for treatment of ST elevation and non-ST elevation myocardial infarction (MI).[1] However, its role in stable coronary disease has been the subject of reappraisal following publication of the COURAGE trial, which showed that, in patients receiving optimal medical therapy, PCI does not improve cardiovascular outcomes, while incremental benefits for quality of life disappear by 36 months.[2,3] A more recent meta-analysis of eight trials of optimal medical therapy versus PCI involving 7,229 patients bears out the COURAGE conclusions by showing no significant differences between the groups with regard to death (9.1% vs 8.9%), non-fatal MI (8.1% vs 8.9%), unplanned revascularisation (30.7% vs 21.4%) and persistent angina (33% vs 29%).[4] Drug-eluting stents (DESs) were used in only a minority of these patients and may have reduced the need for further revascularisation while improving symptomatic responses. Nevertheless, the meta-analysis reinforces contemporary guideline advice for optimal medical treatment as the initial treatment for stable angina.[5] Whether this will change current practice remains to be seen, but early signs are not encouraging. Thus a US registry analysis of patients undergoing PCI before (n = 173,416) and after (n = 293,795) the COURAGE report showed no change in the proportions receiving optimal medical treatment (43.5% vs 44.7%).[6]

PCI versus coronary bypass surgery

The safety of PCI at hospitals without on-site cardiac surgery has been confirmed in two recent reports.[7,8] Add to this the feasibility of PCI in increasingly complex disease and we need look no further to explain the substantial reductions in rates of coronary bypass surgery (CABG) in recent years. A recent US study of revascularisation procedures during 2001-2008 showed a 38% decline in rates of CABG, while PCI decreased by only 4%.[9] Some have questioned whether patients are being appropriately advised according to contemporary guidelines,[10] a US analysis of 500,154 PCIs reporting that, among the 28.9% of cases performed for non-acute indications, only 50.4% were appropriate and that angina was not present in many of the inappropriate cases.[11] In the absence of any evidence of prognostic benefit, there can be no indication for PCI in stable patients without angina. In patients with angina, on the other hand, PCI is as effective as CABG in providing symptom relief at 12 months, judging by a recent report from the SYNTAX investigators.[12] However, CABG may have the advantage of providing prognostic benefit, recent US registry data showing a lower 4-year mortality compared with PCI (16.4% vs 20.8%) in an analysis that adjusted for selection bias.[13] Of course, being a registry study, treatment allocation was not random and any conclusions about relative prognostic benefits require caution. Nevertheless, guideline recommendations are for surgery in complex three-vessel and left main stem disease, although many patients continue to express a preference for PCI, particularly now we have reports of the feasibility and safety of same-day discharge. This is particularly applicable with radial access (or post-procedural deployment of a femoral closure device), and, in a US registry study, 1,339 patients discharged on the same day as their procedure had similar 30-day readmission rates to 105,679 patients who stayed overnight.[14] This is important because it is now

bili otpušteni iz bolnice na dan zahvata, učestalost ponovnog prijma u bolnicu unutar 30 dana je bilo sličan kao kod 105.679 bolesnika koji su u bolnici bili hospitalizirani tijekom jedne noći.[14] To je značajno jer je utvrđeno da je ponovni prijam u bolnicu unutar 30 dana od PCI povezan s znatnim povećanjem stope smrtnosti tijekom jedne godine.[15]

Bolest glavnog stabla lijeve koronarne arterije

O ulasku PCI na teritorij koji je nekad pripadao kardiokirurgiji najbolje svjedoči porast primjene kod bolesti nezaštićenog glavnog stabla lijeve koronarne arterije. Prema podacima iz američkog registra, koji obuhvaća 131.004 pacijenata s bolesti nezaštićenog glavnog stabla lijeve koronarne arterije, udio bolesnika podvrgnutih PCI od 2004. do 2008. godine se povećao s 3,8% na 4,9%. Bolesnici podvrgnuti PCI su bili starije osobe s više komorbiditeta, zbog čega je kod njih registrirana veća stopa bolničke smrtnosti u odnosu na cjelokupnu skupinu (13% naspram 5%).[16] Tehnički napredak od 2008. je dalje doprinio povećanju udjela primjene PCI kod bolesti nezaštićenog glavnog stabla lijeve koronarne arterije, a sada imamo i podatke randomiziranih studija koji potvrđuju sigurnost i učinkovitost postupka. Tako je u korejskoj *PRECOMBAT* studiji uspoređena implantacija DES nasuprot CABG na uzorku od 600 bolesnika, gdje je 8,7% bolesnika s ugrađenim stentom i 6,7% bolesnika podvrgnutih CABG registriran primarni zajednički ishod (kombinacija smrti, MI, moždanog udara i revaskularizacije zbog ishemije unutar 12 mjeseci), što predstavlja značajnu razliku kad govorimo o jednakoj učinkovitosti.[17] Kao i kod prethodnih randomiziranih istraživanja, razlika je uglavnom rezultat većeg broja ponovljene revaskularizacije kod bolesnika s ugrađenim stentom (9,0% naspram 4,2% unutar 2 godine, p = 0,02).

Izbor bolesnika koji imaju bolest glavnog stabla lijeve koronarne arterije za revaskularizaciju temelji se tradicionalno na angiografskoj procjeni, no novija istraživanja navode da bi mjerenje minimalne površine lumena intravaskularnim ultrazvukom (IVUS) moglo biti bolja metoda za odluku kad se radi o bolesnicima koji imaju intermedijarnu angiografsku stenozu u rasponu od 25-60%.[18] Korelacija između minimalne površine lumena i angiografske stenoze je bila loša, ali je mjerenje površine od 6 mm^2 bio dovoljno siguran prag za izbor revaskularizacije, s tim da preživljavanje bez neželjenih događanja kod bolesnika kod kojih je površina mjerenja bila >6 mm^2 i koji nisu podvrgnuti revaskularizaciji, nije bilo lošije nego kod bolesnika kod kojih je površina mjerenja bila <6 mm^2 i koji su podvrgnuti revaskularizaciji. Ovi podaci nisu randomizirani, no ukazuju na korisnu ulogu IVUS u liječenju bolesti glavnog stabla lijeve koronarne arterije.

Stentovi koji izlučuju lijekove i tromboza stenta

Uvođenje metalnih stentova (BMS) krajem prošlog desetljeća znatno je poboljšalo uspješnost i sigurnost PCI, no tek je tehnologija izlučivanja lijeka imala značajan utjecaj na postotak ponovne pojave stenoze. Čini se da je zabrinutost zbog povećanog rizika od tromboze stenta kod DES[19] pretjerana, osobito s današnjom generacijom DES, a potvrđeni su i blagotvorni učinci na pojavu restenoze. Tako je novija retrospektivna analiza usporedila stentove koji izlučuju sirolimus s metalnim stentovima kod dijabetičara i pokazala veliko smanjenje potrebe za ponovnom revaskularizacijom kod ugradnje DES (HR 0,27, 95% CI 0,18 do 0,41), dok se rizik od tromboze stenta nije povećao.[20] Međutim, upravo se stent koji izlučuje everolimus pokazao kao omiljeni DES intervencijskih kardiologa, a meta-analizom 13 randomiziranih ispitivanja provedenih kod 17.101 bolesnika dokazano je da je postotak tromboze tijekom 21,7 mjeseci praćenja bio samo 0,7%, u usporedbi s 1,5% kod bolesnika kojima je ugrađen neki drugi tip DES.[21] Podaci dobiveni meta-analizom 49 ran-

recognised that readmission within 30 days after PCI is associated with a significant increase in 1-year mortality.[15]

Left main stem disease

The trespass of PCI on to territory that was formerly surgical is best illustrated by its increasing application in unprotected left main stem disease. Registry data from the USA for 131,004 patients with unprotected left main stem disease show the proportion treated with PCI increasing from 3.8% to 4.9% between 2004 and 2008. PCI recipients were older with more comorbidities, probably accounting for their higher hospital mortality compared with the overall cohort (13% vs 5%).[16] Technical improvements since 2008 have seen further increases in rates of PCI in unprotected left main stem disease, and we now have randomised trial data confirming its safety and efficacy in selected patients. Thus in the Korean *PRECOMBAT* trial of drug-eluting stenting versus CABG in 600 patients, 8.7% of patients in the stent group and 6.7% in the CABG group met the primary end point (a composite of death, MI, stroke and ischaemia-driven revascularisation at 12 months), a difference significant for the non-inferiority of stenting.[17] As in previous randomised comparisons, the difference was driven largely by a higher rate of repeat revascularisation in stent recipients (9.0% vs 4.2% after 2 years, p = 0.02).

Selection for revascularisation in left main stem disease has traditionally been based on angiographic assessment, but a recent study suggests that measurement of minimum lumen area by intravascular ultrasound (IVUS) might be a better means of selection in patients with ‘intermediate’ angiographic stenoses in the range 25-60%.[18] Correlation between minimum lumen area and angiographic stenosis was poor, but a 6 mm^2 area measurement provided a safe threshold for determining revascularisation, the event-free survival being no worse in the patients with an area measurement >6 mm^2 who did not undergo revascularisation compared with the patients with an area measurement <6 mm^2 who did. These were non-randomised data, but point to a useful role for IVUS in the management of left main coronary artery disease.

DESs and stent thrombosis

The introduction of bare metal stents (BMSs) towards the end of the last decade dramatically improved the performance and safety of PCI, but it required drug-eluting technology to make a significant impact on restenosis rates. Concerns about an increased risk of stent thrombosis with DESs[19] appear to have been exaggerated, particularly with the current generation of DESs, but the beneficial effects on restenosis have been borne out. Thus a recent meta-analysis comparing sirolimus-eluting and bare metal stents in patients with diabetes reported dramatic reductions in the need for repeat revascularisation with the DES (HR 0.27, 95% CI 0.18 to 0.41) without any increase in the risk of stent thrombosis.[20] However, it has been the everolimus-eluting stent that has emerged as the interventionists’ favourite, a meta-analysis of 13 randomised trials including 17,101 patients reporting thrombosis rates of only 0.7% during 21.7 months’ follow-up, compared with 1.5% in patients treated with any other type of DES.[21] A further meta-analysis pooled data from 49 randomised trials including 50,844 patients and came to similar conclusions by showing that everolimus-eluting stents had the lowest risk of stent thrombosis at 30

domiziranih istraživanja kod 50.844 bolesnika imaju slične zaključke, a pokazali su da je kod stentova koji izlučuju everolimus rizik od tromboze unutar 30 dana i 1 godine bio manji nego kod drugih stentova čija je uporaba odobrena u SAD, uključujući i BMS.[22] Razlika u korist stentova koji izlučuju everolimus ostala je značajna i kod razdoblja od 2 godine, kada je rizik od tromboze stenta bio 0,34 (95% CI 0,19 do 0, 62) u usporedbi sa stentovima koji izlučuju paklitaksel i 0,35 (95% CI 0,17 do 0,69) u usporedbi s BMS.

Podaci o DES u graftu v. safene nisu sasvim jasni, no ograničena, dostupna randomizirana ispitivanja ukazuju na bolje rezultate nego kod BMS.[23] Što se tiče primarne PCI, zabrinutost da bi prisustvo tromba moglo pogodovati trombozi u DES nije u potpunosti opravdano, jer je skupna analiza 15 ispitivanja kod IM s elevacijom ST-segmenta (STEMI), u kojima je uspoređivana prva generacija DES s BMS, utvrdila da je primjenom DES potreba za revaskularizacijom ciljnih krvnih žila bila manja (RR 0,51, 95% CI 0,43 do 0, 61), a nije bilo nikakve razlike u učestalosti tromboze stenta kod BMS.[24] Naime, rizik od tromboze stenta se smanjio kod DES (RR 0,80, 95% CI 0,58 do 1,12) tijekom prve godine, no zatim se povećao (RR 2,10, 95% CI 1,20 do 3,69), što je dovelo do zaključka da je rana korist od DES prve generacije kod primarnog PCI kasnije smanjena zbog povećanja rizika od tromboze stenta. DES novije generacije mogu nadoknaditi taj nedostatak, no dok ne budemo imali dovoljno podataka, intervencijski kardiolozi bi trebali pažljivo razmotriti rizike od restenoze i tromboze stenta.

Povećano zanimanje za biorazgradive stentove nastalo je nakon objave izvješća o prvih 12 mjeseci nakon implantacije kod skupine od 56 bolesnika, koje je evaluiralo slikovne prikaze u II. fazi istraživanja.[25] Učestalost pojave restenoze bila je samo 3,5%, a >95% žice stenta je bilo endotelizirano. Nadalje, primijećeno je varijabila dilatacija krvnih žila kao odgovor na acetilkolin, što je upućivalo na povrat normalnih vazomotornih funkcija. S nestrpljenjem se iščekuju rezultati randomiziranih ispitivanja koja su trenutno u fazi planiranja.

Optimalni arterijski pristup

Radijalni pristup kod koronarne angiografije je u širokoj primjeni.[26,27] Jedan od razloga tomu je i sve više dokaza da on smanjuje rizik od krvarenja, a time onda može smanjiti i rizik od smrti kod primarne PCI.[28] Stoga je sveobuhvatna meta-analiza koja se temelji na svim prikupljenim podacima iz randomiziranih studija u primarnoj PCI usporedila femoralni i radijalni pristup te utvrdila da gotovo 50% manju smrtnost kod radijalnog pristupa.[29] Nije jasno može li se taj povoljan učinak općenito primijeniti u svakodnevnoj kliničkoj praksi, no opservacijski podaci potkrepljuju rezultate ispitivanja i upućuju na povoljan učinak radijalnog pristupa kod primarne PCI.[30,31] Prema velikom kanadskom istraživanju provedenom kod 69.214 bolesnika podvrgnutih kateterizaciji srca, druga potencijalna važna prednost radijalnog pristupa jest činjenica da se povezuje i s manjim rizikom od oštećenja funkcije bubrega.[32] Djelovanje nije jasno, a najveće ispitivanje koje je usporedilo radijalni i femoralni pristup, studija *RIVAL*, nije dalo jasnu prednost niti jednom pristupu, iako se pokazalo da podskupina podvrgnuta primarnom PCI preferira radijalni pristup.[33] Na temelju trenutno dostupnih dokaza, izbor između radijalnog i femoralnog pristupa treba donijeti za svakog pojedinca posebno, uzimajući u obzir iskustvo intervencijskog kardiologa, rizik od krvarenja i želju bolesnika.

Ima li novosti u antiagregacijskom liječenju?

Dvojna antiagregacijska terapija primjenom acetilsalicilatne kiseline (ASK) i klopidogrela, kod bolesnika podvrgnutih PCI, prema preporukama iz smjernica i dalje ima prednost. Veznao uz klopidogrel, skupna analiza dostupnih podataka preporuča početnu dozu od 600 mg, za koju se pokazalo da

days and 1 year compared with other stents approved for use in the USA, including BMSs.[22] The difference in favour of everolimus-eluting stents remained significant at 2 years when the odds of stent thrombosis was 0.34 (95% CI 0.19 to 0.62) compared with paclitaxel-eluting stents and 0.35 (95% CI 0.17 to 0.69) compared with BMSs.

Data on DESs in saphenous vein grafts are somewhat less clear, but the limited available randomised trials do suggest superiority compared with BMSs.[23] For primary PCI, concerns that the thrombotic environment might predispose to DES thrombosis have not been fully realised, a pooled analysis of 15 STEMI trials comparing first-generation DESs with BMSs reporting a lower requirement for target vessel revascularisation with DESs (RR 0.51, 95% CI 0.43 to 0.61), with no difference in the rate of stent thrombosis compared with BMSs.[24] Indeed, the risk of stent thrombosis during the first year was reduced for DESs (RR 0.80, 95% CI 0.58 to 1.12) but increased thereafter (RR 2.10, 95% CI 1.20 to 3.69), suggesting that the early benefit of first-generation DESs in primary PCI is offset by a later increase in the risk of stent thrombosis. Newer-generation DESs may overcome this drawback, but, until we have sufficient data, operators should carefully weigh the differential risk of reste- nosis and stent thrombosis between the two stent types.

Interest in bioresorbable stents has been enhanced by reports from a phase II evaluation of imaging data 12 months after implantation in 56 patients.[25] The restenosis rate was only 3.5%, and >95% of the stent struts were endothelialised. Moreover, variable coronary dilatation in response to acetylcholine was observed, indicating some return of normal vasomotor responses. The results of randomised trials now in the planning stage are eagerly awaited.

Optimal arterial access

Radial access for coronary angiography has now achieved widespread application.[26,27] One reason is the accumulating evidence that it reduces bleeding risk and, perhaps because of this, may reduce mortality in primary PCI.[28] Thus a comprehensive meta-analysis pooling all the data from randomised primary PCI trials comparing femoral with radial access showed a nearly 50% mortality reduction in the radial group.[29] Whether this beneficial effect is generalisable to everyday clinical practice is unclear, but observational data support the trial results and indicate benefit of radial access for primary PCI.[30,31] Another potentially important advantage of radial access is its association with a reduced risk of kidney injury, as reported in a large Canadian study of 69,214 patients undergoing cardiac catheterisation.[32] The mechanism is unclear and the largest trial comparing radial and femoral access, the RIVAL trial, did not show a clear advantage for either access route, although radial access appeared preferable in the subgroup undergoing primary PCI.[33] On the basis of current evidence, the choice between radial and femoral access should be individualised taking into account operator experience, bleeding risk and patient preference.

Antiplatelet therapies — what's new?

In patients undergoing PCI, dual antiplatelet therapy with aspirin and clopidogrel remain central to guideline recommendations. For clopidogrel, a pooled analysis of available data favoured a loading dose of 600 mg, which was associated with a 34% reduction in the rate of major adverse car-

smanjuje postotak velikih neželjenih kardioloških događaja (MACE) za 34%, a da ne povećava rizik od značajnog krvarenja, za razliku od početne doze 300 mg.[34] Sada imamo dokaze iz randomiziranih istraživanja koja potvrđuju da, za razliku od 300 mg, početna doza od 600 mg kod primarne PCI znatno smanjuje veličinu infarkta, mjerenu prosječnom vrijednosti CK-MB tijekom 72h (2.070 naspram 3.029 ng/ml).[35] Dugotrajnija terapija ASK i klopidogrelom preporuča se obično nakon PCI i kod stabilnih bolesnika te kod bolesnika s akutnim koronarnim sindromom (ACS), iako je antiagregacijski učinak klopidogrela varijabilan, a visoka rezidualna trombocitna reaktivnost je utvrđena kod 14,7% do 26,9% bolesnika, ovisno o korištenom testu.[36] Dio tih varijacija u antiagregacijskoj prijemljivosti proizlazi iz činjenice da je klopidogrel prolijek te da enzimi koji formiraju njegov aktivni metabolit pokazuju funkcionalno različite polimorfizme. Međutim, prema istraživanju provedenom u Nizozemskoj kod 1.069 bolesnika koji su prvo liječeni klopidogrelom, a zatim su podvrgnuti elektivnoj PCI, stanje nositelja alela s reduciranom funkcijom CYP2C19 je objasnilo samo jedan dio varijacija u trombocitnoj reaktivnosti (13% do 20,6%), ovisno o korištenom testu.[37] Jedan od načina na koji se visoka rezidualna trombocitna reaktivnost kod varijacija nositelja alela s reduciranom funkcijom CYP2C19 može modificirati je primjena antiagregacijskih lijekova koji se metaboliziraju na različit način, što su potvrdili i znanstvenici iz Koreje u istraživanju provedenom u sklopu randomiziranog istraživanja *CILON-T*.[38] Kod bolesnika s varijacijama nositelja alela s reduciranom funkcijom CYP2C19, koji su nasumično odabrani za dvojnu antiagregacijsku terapiju i cilostazol (selektivni inhibitor fosfodiesteraze tipa 3) registrirano je znatno smanjenje rezidualne trombocitne reaktivnosti, u usporedbi s bolesnicima koji su primili samo ASK i klopidogrel. Djelovanje cilostazola nije zabilježeno kod polimorfizma nenositelja alela s reduciranom funkcijom. Alternativni način modificiranja visoke rezidualne trombocitne reaktivnosti nakon PCI je povećanje doze klopidogrela. Međutim, to se nije pokazalo učinkovitim u studiji *GRAVITAS*, jer je ukupni šestomjesečni zajednički ishod od kardiovaskularne smrti, MI i tromboze stenta bio identičan u randomiziranim skupinama s visokom (150 mg/dan) i standarnom, niskom (75 mg/dan) dozom klopidogrela.[39]

Prema trenutnim preporukama iz smjernica, klopidogrel bi trebalo prestati primjenjivati 12 mjeseci nakon ugradnje DES, po završetku endotelizacije, jer se smanjio rizik od tromboze. Zabrinjava činjenica da je određeni broj kasnih kliničkih događaja povezan s ovom preporukom, a prema nedavnom britanskom istraživanju,[40] to je možda zbog povećane aktivacije trombocita uzrokovane arahidonskom kiselinom, što potvrđuje sve veći broj dokaza da klopidogrel ima neko antiagregacijsko djelovanje neovisno od ASK. Naime, ukazuje se da bi bilo racionalno prekinuti primjenu ASK, a ne klopidogrela jednu godinu nakon ugradnje stenta.[41] Taj će problem uskoro biti ispitan u velikom randomiziranom istraživanju *GLOBAL-LEADERS*. Ograničenja dvojne antiagregacijske terapije s ASK i klopidogrelom pokazana su dodatno i u studiji *on-TIME-2,* u kojem su bolesnici koji su podvrgnuti primarnoj PCI randomizirani na dodatnu primjenu tirofibana ili placeba prije hospitalizacije.[42] Dodavanje tirofibana je rezultiralo učinkovitijom inhibicijom trombocita nego sam ASK ili klopidogrel, a to je dovelo do smanjenja broja MACE i rane tromboze stenta. *On-TIME-2* dalje potkrepljuje smjernice i preporuke vezane za ranu inhibiciju glikoproteina IIb/IIIa uz dvojnu antiagregacijsku terapiju kod bolesnika liječenih primarnom PCI.

Novi inhibitori receptora P2Y12

Primjenu inhibitora receptora P2Y12, prasugrela i tikagrelora, preporučena je u smjernicama za zbrinjavanje ACS[43] te-

diac events (MACE) without any increase in the risk of major bleeding compared with a 300 mg loading dose.[34] Now we have randomised trial evidence confirming that, compared with the 300 mg loading dose, the 600 mg dose in primary PCI is associated with significant reductions in infarct size, measured by median CKMB mass over 72 h (2,070 vs 3,029 ng/ml).[35] Continuing therapy with aspirin and clopidogrel is usually recommended after PCI in both stable and patients with acute coronary syndromes (ACS), but the antiplatelet effect of clopidogrel is variable, and high on-treatment platelet reactivity can be demonstrated in 14.7-26.9% of patients, depending on the test used.[36] Part of this variability in antiplatelet responsiveness is explained by the fact that clopidogrel is a prodrug, and the enzymes that form its active metabolites exhibit functionally distinct polymorphisms. However, a study from the Netherlands of 1,069 clopidogrel-pretreated patients undergoing elective PCI found that loss-of-function CYP2C19 carrier status explained only part of the variability in platelet reactivity (13.0-20.6%), depending on the test used.[37] One approach to modifying high on-treatment platelet reactivity in carriers of loss-of-function CYP2C19 variants is to use antiplatelet drugs metabolised by different pathways, and this was confirmed by investigators from Korea in a substudy of the CILON-T randomised trial.[38] In patients with loss-of-function CYP2C19 variants who were randomised to dual antiplatelet therapy plus cilostazol, a selective phosphodiesterase-3 inhibitor, on-treatment platelet reactivity was significantly reduced compared with patients who received only aspirin and clopidogrel. This effect of cilostazol was not seen in non-carriers of the loss-of-function polymorphism. An alternative approach for modifying high on-treatment platelet reactivity after PCI is to increase the dose of clopidogrel. However, this was found ineffective in the GRAVITAS trial, the 6-month rate of the composite of cardiovascular death, MI and stent thrombosis being identical for groups randomised to high-dose (150mg daily) or standard-dose (75mg daily) clopidogrel.[39]

Current guideline recommendations are for clopidogrel to be stopped 12 months after DES deployment when endothelialisation is complete, reducing the risk of thrombosis. Worryingly, a clustering of late clinical events has been associated with this policy, perhaps because of an increase in arachidonic acid-induced platelet activation as reported in a recent UK study,[40] lending support to the accumulating evidence that clopidogrel exerts some of its antiplatelet effects via this pathway, independently of aspirin. Indeed, it has been suggested that discontinuation of aspirin instead of clopidogrel might be more rational 1 year after stenting.[41] This question will soon be tested in the large GLOBAL-LEADERS randomised trial. The limitations of dual antiplatelet therapy with aspirin and clopidogrel have been further illustrated by the on-TIME-2 trial, in which patients undergoing primary PCI were randomised to additional prehospital tirofiban or placebo.[42] The addition of tirofiban produced more effective platelet inhibition than aspirin and clopidogrel alone, and this was associated with a reduction in MACE and early stent thrombosis. On-TIME-2 lends further support to guideline recommendations for early glycoprotein IIb/IIIa inhibition together with dual antiplatelet therapy in patients undergoing primary PCI.

Newer P2Y12 receptor inhibitors

These include prasugrel and ticagrelor, which now have guideline indications in ACS[43] based on the TRITON and PLATO randomised trials, which were the subject of recent

meljem randomiziranih ispitivanja *TRITON* i *PLATO*, a bila je to i tema nedavno objavljenog preglednog članka.[44] U ispitivanju *TRITON* bolesnici liječeni primjenom PCI radi ACS randomizirani su u skupine liječene klopidogrelom ili prasugrelom tijekom 12 mjeseci od zahvata.[45] Vezano uz primarni zajednički ishod, prasugrel se pokazao boljim od klopidogrela, uglavnom zbog periproceduralnog MI. Također je znatno smanjen rizik od tromboze stenta. Međutim, uz dobrobit, ustanovljen je veći rizik od značajnih i manjih krvarenja. U studiji *PLATO*, koje je usporedila tikagrelor s klopidogrelom kod bolesnika s ACS koji su bili liječeni farmakološki lili primjenom PCI,[46] tikagrelor se pokazao boljim kod ukupnog primarnog zajedničkog cilja od *MACE*. Manja krvarenja su bila češća kod tikagrelora, a rizik od značajnog krvarenja je bio sličan onome kod klopidogrela. Ova randomizirana istraživanja potvrdila su da intenzivnija inhibicija trombocita s prasugrelom ili tikagrelorom daje bolje kliničke rezultate kod ACS, ali uz veći rizik krvarenja, osobito, kako se čini, s prasugrelom. Prednost kliničkih ishoda oba lijeka je mala u apsolutnom smislu, što je povuklo važno pitanje financijske isplativosti. Prema američkoj evaluaciji prasugrela, radi se o "financijski privlačnoj strategiji liječenja",[47] no novija tehnološka ocjena NICE bila je opreznija te je preporučila prasugrel kao opciju kod bolesnika sa STEMI ako je potreban hitna primarna PCI (zbog njegovog brzog djelovanja u usporedbi s klopidogrelom), kod dijabetesa ili ako se tijekom terapije klopidogrelom pojavila tromboza stenta.[43] Postoji zabrinutost oko njegove troškovne učinkovitosti u drugim situacijama. Nedavna zdravstveno-ekonomska analiza koja se temeljila na ispitivanju PLATO zaključila je da je liječenje bolesnika s ACS primjenom tikagrelora tijekom 12 mjeseci povezana s troškovima poboljšane kvalitete godina života (QALY) ispod općenito prihvaćenog praga isplativosti.[48]

Bivalirudin i heparin

Bivalirudin je sada dostupan za liječenje ACS, a svoju središnju poziciju u primarnoj PCI stekao je vrlo brzo.[49] To je direktan inhibitor trombina s dodatnom aktivnosti protiv aktivacije trombocita trombinom, a pokazao se učinkovitiji od kombiniranog režima koji uključuje heparin i inhibitor glikoproteina IIb/IIIa u istraživanju *HORIZONS-AMI,* zahvaljujući manjoj učestalosti značajnih krvarenja (4,9% naspram 8,3%). Ukupna smrtnost unutar 30 dana bila je niža, a sada imamo i podatke trogodišnjeg praćenja koji potvrđuju kontinuirano smanjenje smrtnosti (5,9% naspram 7,7%), na temelju čega je bivalirudin preporučen u smjernicama kod primarne PCI.[50] Klinička dobrobit bivalirudina vezana je za njegovu troškovnu učinkovitost s obzirom da su cjeloživotni troškovi bolesnika u Velikoj Britaniji niži za 267 GBP u odnosu na inhibitore glikoproteina IIb/IIIa.[51] Mali porast u broju tromboze stenta kod bolesnika koji su dobivali bivalirudin nije registriran u bolesnika koji su prethodno dobili heparin, a podaci iz registra *SCAAR* ukazuju na to da kombinacija bivalirudina i prethodne primjene heparina smanjuje smrtnost,[52] radi čega su i autori uvodnika preporučili dvojnu terapiju kod bolesnika liječenih primarnom PCI.[53]

Nefrakcionirani heparin i dalje se preporuča kao lijek klase I za primjenu tijekom PCI, no nova meta-analiza koje se temelji na skupnim podacima iz 23 istraživanja pokazuju da enoksaparin znatno smanjuje zajednički ishod od smrti, MI i značajnog krvarenja u usporedbi s nefrakcioniranim heparinom.[54] Najveća korisnost je bila kod primarne PCI, ali također i kod PCI bez elevacije ST-segmenta te stabilne angine pektoris. Čini se da je sada pravo vrijeme za promjenu smjernica u korist heparina niske molekularne težine tijekom PCI.

review.[44] TRITON randomised patients undergoing PCI for ACS to either clopidogrel or prasugrel therapy for 12 months after the procedure.[45] Prasugrel showed superiority over clopidogrel for the composite primary end point, driven mainly by periprocedural MI. It also showed significant risk reduction for stent thrombosis. However, these benefits came with an increased risk of major and minor bleeding. In the PLATO trial of ticagrelor versus clopidogrel in patients with ACS managed medically or with PCI,[46] ticagrelor was superior with regard to the primary composite end point of MACE, but, while minor bleeding was more common with ticagrelor, the major bleeding risk was comparable to that with clopidogrel. These randomised trials have confirmed that more intensive platelet inhibition with prasugrel or ticagrelor delivers better clinical outcomes in ACS, although there is a bleeding penalty, particularly it seems for prasugrel. The clinical outcome advantage for both drugs is small in absolute terms, raising important questions about cost-effectiveness. A US evaluation for prasugrel concluded it was 'an economically attractive treatment strategy',[47] but a more recent National Institute for Health and Clinical Excellence (NICE) technology assessment was more guarded, recommending prasugrel as an option in patients with STEMI if immediate primary PCI is necessary (based on its rapid onset of action compared with clopidogrel), or if diabetes is present or if stent thrombosis has occurred during clopidogrel treatment.[43] However, concern was expressed about its likely cost-effectiveness in other situations. A recent health-economic analysis based on the PLATO study concluded that treating patients with ACS with ticagrelor for 12 months is associated with a cost per QALY (quality-adjusted life year) below generally accepted thresholds for cost-effectiveness.[48]

Bivalirudin and heparin

Bivalirudin is now available for treatment of ACS and has rapidly gained a central role in primary PCI.[49] It is a direct thrombin inhibitor with additional activity against thrombin-mediated platelet activation that showed superiority over a combined regimen of heparin plus a glycoprotein IIb/IIIa inhibitor in HORIZONS-AMI, due largely to a lower rate of major bleeding (4.9% vs 8.3%). All-cause mortality was lower at 30 days, and we now have 3-year follow-up data confirming persistent mortality benefit (5.9% vs 7.7%), ensuring a guideline recommendation for bivalirudin in primary PCI.[50] The clinical benefits of bivalirudin have also been associated with cost-effectiveness, patient lifetime costs in the UK being 267 lower than for glycoprotein IIb/IIIa inhibitors.[51] A small increase in rates of stent thrombosis with bivalirudin was not seen in patients pretreated with heparin, and the mortality benefits of combining bivalirudin with heparin pretreatment have since been reported from the SCAAR registry,[52] leading the editorialist to recommend dual therapy in patients undergoing primary PCI.[53]

Unfractionated heparin retains a class 1 recommendation for use during PCI, but a recent meta-analysis of pooled data from 23 studies has shown that enoxaparin is associated with significant reductions in the composite of death and MI and in major bleeding rates compared with unfractionated heparin.[54] These benefits were greatest for primary PCI, but were also seen in PCI for non-ST elevation MI and stable angina. The time may be right for a change of policy in favour of low-molecular-weight heparin during PCI.

Intravaskularni slikovni prikaz — dobrobit za kliničku primjenu?

Korisnost IVUS u kliničkoj primjeni kod PCI je i dalje kontroverzna, iako je analiza skupnih podataka iz sedam randomiziranih studija u kojima su primjenjeni BMS došla do zaključka da je kod IVUS vođene PCI manji rizik od in-stent restenoze.[55] IVUS je također počeo dobivati na važnosti u procjeni lezija glavnog stabla lijeve koronarne arterije kod revaskularizacije.[18] Osobito važnim alatom pokazao se IVUS u istraživanjima za ocjenu neinvazivnog slikovnog prikaza koronarne stenoze.[56] Tako je u novijem istraživanju koje je usporedilo koronarnu CT angiografiju i IVUS u mjerenju volumena plaka pokazano da je slaganje između te dvije metode bilo vrlo slabo (granice slaganja po Bland-Altmanu od -67 do +65 mm^3), što ukazuje na ograničenja koronarnog CT u ocjeni proširenosti KBS.[57] Dok je sposobnost slikovnog prikaza kroz stijenku koronarne arterije velika prednost IVUS, tehnologija je ograničena rezolucijom slike koja je puno lošija u usporedbi s optičkom koherentnom tomografijom (OCT). U podstudiji istraživanja *ODESSA* primjenom OCT registrirana je suboptimalna uporaba stentova kao nedovoljna ekspanzija stenta na razini pojedinih žica stenta, što je detalj koji se kod IVUS ne bi nikako registrirao.[58] OCT se sve više koristi u procjeni endotelizacije žica stenta, a novije japansko istraživanje implantacije stentova koji izlučuju everolimus pokazalo je da je od 5.931 ocjenjenih stentova 98,4% endotelizirano 8 mjeseci nakon implantacije, što znači nizak rizik od tromboze kod ove druge generacije DES.[59]

Intravaskularni slikovni prikaz se također koristi u ocjenjivanju stabilnosti plaka, a ispitivanje *PROSPECT* je potvrdilo da IVUS može razlikovati stabilne od nestabilnih plakova i da može predvidjeti nepovoljne događaje.[60] Glavna karakteristika nestabilnog plaka je ateroskleroza s tankom kapom, a noviji podaci podsjećaju na činjenicu da upalni proces uvelike utječe na nestabilnost, dok ispitivanje OCT pokazuje da postoji jasna veza između debljine kape plaka i upalnih markera plaka, primjerice visoko osjetljivog C-reaktivnog proteina.[61]

Tehnički aspekti ugradnje stenta — što smo naučili?

Preklapanje stentova

Ponovna endotelizacija dijelova stentova koji se preklapaju je sporija, pa stoga većina intervencijskih kardiologa radije koristi jedan stent.[58] Međutim, u klničkoj praksi preklapanje stentova je često neizbježno, a kad se radi o DES, dobro je poznato da bi se trebali koristiti stentovi iste vrste kako bi se izbjeglo izlučivanje različitih farmakoloških spojeva u dijelovima koji se preklapaju. Korejsko istraživanje provedeno kod 1.080 bolesnika s preklapanjem DES dovelo je to u pitanje.[62] Istraživanje je pokazalo da su srčana smrt, MI i revaskularizacija ciljne lezije imali sličnu učestalost bez obzira na to jesu li DES bili homogeni ili heterogeni.

Ugradnja stenta u bifurkaciji

Nekoliko istraživanja je pokazalo da primjena jednog stenta u glavnoj krvnoj žili daje jednake, a često i bolje, rezultate od uporabe dva stenta. Zajednička analiza rezultata istraživanja *NORDIC Bifurcation Study i British Bifurcation Coronary Study* pokazala je da se kod bolesnika randomiziranih na "jednostavnu" ugradnju stenta u glavnu krvnu žilu ukupni ishod MACE nakon 9 mjeseci iznosio 10,1% u usporedbi s 17,3% kod bolesnika podvrgnutih kompleksnoj ugradnji stenta u dvije krvne žile (p=0,001).[63] Međutim, i dalje ostaje

Intravascular imaging — clinical benefit?

The clinical benefit of using IVUS to guide PCI remains controversial, although a pooled analysis of seven randomised BMS trials has concluded that IVUS-guided PCI is associated with a reduced risk of in-stent restenosis.[55] IVUS is also finding a role in assessing left main stem lesions for revascularisation.[18] As a research tool, however, and for validation of non-invasive imaging of coronary stenosis, IVUS has proved particularly valuable.[56] Thus, in a recent study comparing coronary CT angiography and IVUS for plaque volume measurements, there was only modest agreement between the two methods (Bland-Altman limits of agreement -67 to +65 mm^3), reflecting the limitations of coronary CT for assessing the extent of coronary disease.[57] While the ability to image across the coronary arterial wall is a particular strength of IVUS, the technology is limited by image resolution, which is considerably inferior to optical coherence tomography (OCT). In a substudy of ODESSA, for example, suboptimal stent deployment was identified by OCT at the level of individual stent struts, a detail that could never be reproduced by IVUS.[58] Increasingly, OCT is being used to assess stent strut endothelialisation, a recent Japanese study of everolimus-eluting stent implantation showing that, of 5,931 struts assessed, 98.4% were endothelialised 8 months after implantation, an observation reflected in the low thrombotic risk for these second-generation DESs.[59]

Intravascular imaging has also been used to assess plaque stability, the PROSPECT trial confirming that IVUS can differentiate stable from unstable plaque and predict adverse events.[60] A key feature of unstable plaque is thin-cap atherosclerosis, and recent data remind us that the inflammatory environment is an important determinant of instability, an OCT study showing a clear association between the cap thickness of plaques and inflammatory plasma markers such as high-sensitivity C-reac- tive protein.[61]

Technical aspects of stenting — what have we learnt?

Overlapping stents

Re-endothelialisation of overlapping stent segments is slower, and most operators prefer single stent deployment for that reason.[58] However, in the real world, overlapping stent deployment is often unavoidable, and, for DESs, the conventional wisdom has been that homogeneous stents should be used to avoid elution of different pharmacological compounds within the overlapping segment. This has now been challenged by a Korean study of 1080 patients who received overlapping DESs.[62] The study showed that cardiac death, MI or target lesion revascularisation occurred with similar frequency regardless of whether the DESs were homogeneous or heterogeneous.

Bifurcation stenting

Several studies have shown that a single, main vessel stent deployment provides outcomes that are comparable and often superior to two-stent deployment. Thus a combined analysis of the NORDIC Bifurcation Study and the British Bifurcation Coronary Study showed that, in patients randomised to 'simple' main vessel stenting, the composite MACE end point at 9 months occurred in 10.1% of patients compared with 17.3% of patients who underwent complex two-vessel stenting (p=0.001).[63] However, questions remain,

upitna vrijednost konačne inflacije priljubljenih balona u bifurkaciji nakon ugradnje stenta u glavnu krvnu žilu. Taj je problem bio predmet velikog istraživanja kod 1.055 bolesnika podvrgnutih ugradnji stenta u bifurkaciji.[64] Usporedna analiza u skupinama bolesnika sa i bez konačne inflacije priljubljenih balona utvrdila je da se kod bolesnika kod kojih je izvršena konačna inflacija balona registrirana veća učestalost MACE i revaskularizacije ciljne lezije, većinom na glavnoj žili, nego u skupini kod kojih konačna inflacija priljubljenih balona nije rađena. Konačna inflacija priljubljenih balona, koja može učiniti više zla nego dobra, nije više u fokusu.

Infarkt miokarda — test visoko osjetljivog troponina

Najvažniji element u dijagnozi akutnog MI je dokazati povišenu i promjenjivu koncentraciju troponina tijekom prvih 24 sata nakon nastupa simptoma. Dostupnost testova troponina visoke osjetljivosti (hsTn) vjerojatno će doprinijeti smanjenju dijagnostičkih pragova, što će uvelike utjecati na kliničko liječenje i na srčane ishode. Tako je u novijem istraživanju kod 1.038 bolesnika sa sumnjom na ACS izmjerena vrijednost hsTn-I koja je bila ispod ranijih granica otkrivanja (0,20 ng/ml), pokazala različite stupnjeve povezanosti sa smrtnim ishodom i nefatalnim MI.[65] Kod daljnjih 1.054 bolesnika dijagnostički prag smanjen je na 0,05 ng/ml, a nadležni liječnici su prema tome trebali izmijeniti liječenje. Stopa smrtnosti i ponavljanja MI snizila se s 39% na 12% kod bolesnika s koncentracijom troponina od 0,05 do 0,19 ng/ml, što su granice koje ne bi mogle biti otkrivene konvencionalnim testovima troponina. Istraživači su zaključili da bi smanjenje dijagnostičkog praga korištenjem testova hsTn moglo izdvojiti visoko rizične bolesnike kod kojih se sumnja na ACS te znatno poboljšati njihovu prognozu.

Uvijek se preporučalo da bi se razina dijagnostičkog praga određena za troponin trebala temeljiti na koeficijentu varijacije ≤10%, no nove smjernice preporučaju usvajanje vrijednosti 99. centila bez obzira na nepreciznost testa.[66] Procjena potencijalnog kliničkog učinka te promjene u smjernicama je napravljena na ranije spomenutoj skupini,[65] s tim da se ovaj puta koristio dijagnostički prag od 0,012 μg/l (koeficijent varijacije je 20,8%).[67] Nakon 1 godine bolesnici s koncentracijom troponina od 0,012-0,049 μg/l, kod kojih prije nije mogao biti dijagnosticiran MI, imali su više izgleda da dožive smrtni ishod ili budu primljeni u bolnicu zbog ponovljenog MI nego kod bolesnika s koncentracijama troponina <0,012 μg/l (13% naspram 3%, p<0,001). Autori su zaključili da bi smanjenje dijagnostičkog praga na 99. centil i toleriranje veće nepreciznosti testiranja izdvojilo više bolesnika kod kojih postoji visoki rizik od ponavljanja MI i smrtnog ishoda, no povećalo bi i dijagnosticiranje MI za 46%. Još treba utvrditi hoće li ponovna klasifikacija tih bolesnika i njihovo liječenje u skladu s konvencionalnim smjernicama za MI poboljšati ishode.

Testovi hsTn neće samo smanjiti dijagnostičke pragove za akutni MI, nego mogu omogućiti i izdvajanje bolesnika s naizgled stabilnom KBS koji imaju vulnerabilne koronarne lezije.[68] Tako je novije istraživanje pokazalo jaku povezanost između hsTn-T i stanja nekalcificiranog plaka (r = 0,79, p<0,001) kod 124 bolesnika sa stabilnom anginom pektoris koji su bili podvrgnuti CT angiografiji, a bolesnici s remodeliranim nekalcificiranim plakom su imali najviše vrijednosti hsTn-T.[69] Testovi hsTn se već primjenjuju u kliničkoj praksi kod ranog dijagnosticiranja MI u pacijenata s bolovima u prsnom košu u hitnoj službi. U studiji *Randomised Assess-*

particularly concerning the value of final kissing balloon inflations across the bifurcation following main-vessel stenting. This was addressed in a large observational study of 1055 patients undergoing bifurcation stenting.[64] A comparative propensity analysis of patients who did and did not have final kissing balloon inflations showed a higher incidence of MACE and target lesion revascularisation, mostly in the main vessel, for patients who had final kissing balloon inflations. The pendulum therefore has now swung away from final kissing balloon inflation, which may cause more harm than good.

Myocardial infarction — high-sensitivity troponin assays

Central to the diagnosis of acute MI is the demonstration of a raised and changing troponin concentration in the first 24 h after symptom onset. The availability of high-sensitivity troponin (hsTn) assays is likely to see diagnostic thresholds fall, with important implications for clinical management and cardiac outcomes. Thus, in a recent study in which hsTn-I was measured in 1,038 patients with suspected ACS, values below the previous limit of detection (0.20ng/ml) showed graded association with death or non-fatal MI.[65] In a further 1,054 patients, the diagnostic threshold was lowered to 0.05 ng/ml, and attending physicians were invited to modify their management accordingly. Rates of death and recurrent MI fell from 39% to 12% among patients with troponin concentrations 0.05-0.19 ng/ml, levels that would have been undetectable with conventional troponin assays. The investigators concluded that lowering the diagnostic threshold using hsTn assays has the potential to identify many high-risk individuals with suspected ACS and produce major improvements in their prognosis.

It has always been the recommendation that the diagnostic threshold level chosen for troponin should be based on a coefficient of variation of ≤10%, but new guidance is for the 99th centile value to be adopted regardless of assay imprecision.[66] The potential clinical impact of this change in guidance was evaluated in the same cohort as reported previously,[65] this time using a diagnostic threshold of 0.012 μg/l (coefficient of variation 20.8%)[67] At 1 year, patients with troponin concentrations of 0.012-0.049 μg/l, who previously would have escaped a diagnosis of MI, were more likely to be dead or readmitted with recurrent MI than those with troponin concentrations <0.012 μg/l (13% vs 3%, p<0.001). The authors concluded that lowering the diagnostic threshold to the 99th centile and accepting greater assay imprecision would identify more patients at high-risk of recurrent MI and death, but increase the diagnosis of MI by 46%. It remains to be established whether reclassification of these patients and treating them according to conventional MI guidelines will improve their outcomes.

hsTn assays will not only cause diagnostic thresholds for acute MI to fall, but may also allow identification of patients with apparently stable coronary disease who have vulnerable coronary lesions.[68] Thus a recent study has shown a strong correlation between hsTn-T and non-calcified plaque burden (r = 0.79, p<0.001) in 124 patients with stable angina undergoing CT angiography, patients with remodelled non-calcified plaque having the highest hsTn-T values.[69] hsTn assays have already found clinical application for the early diagnosis of MI in patients with chest pain attending the emergency department. In the Randomised Assessment of Treatment using Panel Assay of Cardiac Markers (RAT-

ment of Treatment using Panel Assay of Cardiac Markers (RAPTAC) primjena hsTn-I u nizu biomarkera omogućilo je uspješno otpuštanje iz bolnice 32% bolesnika, u usporedbi s 13% bolesnika koji su prošli standardni dijagnostički postupak.[70] Osim što imaju ključnu ulogu za dijagnozu, vrijednost troponina također određuje težinu MI, a prema izvještaju koji se temelji na rezultatima GRACE registra[71], koji je obuhvatio 16.318 bolesnika s MI bez elevacije ST-segmenta, svako deseterostruko povećanje vrijednosti troponina bilo je povezano s postupnim povećanjem učestalosto ventrikulskih aritmija, zatajivanja srca, kardiogenog šoka i smrti.[72]

Lezije koje nisu odgovorne za akutni koronarni sindrom

Važnost spašavanja miokarda tijekom akutne faze infarkta proizlazi iz činjenice da prognoza uvelike ovisi o krajnjoj veličini infarkta. Stoga bi mogli postaviti hipotezu da je liječenje svih značajnih lezija korisno. Jedno od prvih randomiziranih ispitivanja primarne PCI koje je testiralo tu hipotezu objavljeno je prošle godine. Od 214 bolesnika koji imaju višežilnu KBS, učestalost nepovoljnih događaja tijekom prosječnog razdoblja praćenja od 2,5 godine bila je viša kod PCI na samo odgovornoj leziji, nego kod višežilne intervencije, bez obzira na to je li PCI izvršen tijekom prvog zahvata ili kasnije u nekoj od odgođenih faza.[73] Međutim, ispitivanje je bilo malo i ne nudi definitivan zaključak, a novija meta-analiza je dala prednost primarnoj PCI na vodećoj leziji te odgođenom zahvatu na lezijama koje nisu odgovorne za akutni infarkt.[74] Ovo je preporučeno i u smjernicama te je dobilo potvrdu analizom opservacijskih podataka iz *HORIZONS-AMI* studije, u kojem su ishodi liječenja 275 bolesnika podvrgnutih implantaciji stenta u jednom zahvatu uspoređivani s ishodima liječenja 393 bolesnika podvrgnutih ugradnji stenta u odgođenim zahvatima.[75] Bolesnicima podvrgnutim jednom zahvatu ugrađen je znatno veći broj stentova, a imali su i znatno veću smrtnost unutar 12 mjeseci (9,2% naspram 2,3%) nego bolesnici podvrgnuti odgođenim zahvatima. Težina dokaza je sada čvrsto na strani ugradnje stenta tijekom primarne PCI samo za odgovornu leziju.

Veličina infarkta i spašavanje miokarda

Cirkadijalni ritam na početku MI je dobro poznat, s tim da su jutarnji sati razdoblje najvećeg rizika. Zanimljivo je da veličina infarkta pokazuje slične cirkadijalne promjene, a retrospektivna analiza 811 bolesnika sa STEMI pokazuje da vrijednost kreatin-kinaze (CK) i troponina I dosežu najviše vrijednosti između 6 sati ujutro i podneva.[76] Spašavanje miokarda primjenom reperfuzijske terapije pomoću PCI je osnovni način terapeutskog ograničavanja veličine infarkta, koji se sada može mjeriti kardiovaskularnom magnetskom rezonancijom (CMR). Istraživanje provedeno kod 208 bolesnika sa STEMI potvrdilo je da je opseg spašavanja, oslikavanjem pomoću CMR usko povezan s dugoročnom prognozom, a bolesnici čiji je indeks spašavanja miokarda (MSI) bio iznad prosječne razine imali su manji broj nepovoljnih kardiovaskularnih događaja (7 naspram 26) i smrti (2 naspram 12) nakon 18,5 mjeseci, u usporedbi s bolesnicima čiji je MSI bio ispod prosječne razine.[77] Međutim, i sama reperfuzija miokarda može pogoršati ozljedu nizom mehanizama koji uključuju i intersticijalno krvarenje. Ono se može otkriti putem CMR, a nalazi se kod 25% bolesnika sa STEMI koji su uspješno liječeni primarnom PCI.[78] Prisutnost krvarenja je bio neovisan predskazatelj nepovoljnog remodeliranja, što se vidjelo u povećanom završnom sistoličkom volumenu u lijevoj klijetki (LV) unutar 3 mjeseca. Intersticijalno krvarenje kao prediktor remodeliranja LV je još više dobilo na važnosti u PAC) trial, the use of hsTn-I within a panel of biomarkers allowed successful discharge of 32% of patients compared with 13% of patients receiving standard diagnostic procedures.[70] Beyond their central role for diagnosis, troponins also provide a measure of the severity of MI, and, in a report from the GRACE registry,[71] incorporating 16,318 patients with non-ST elevation MI, each 10-fold increase in the troponin ratio was associated with stepwise increments in ventricular arrhythmias, heart failure, cardiogenic shock and death.[72]

Non-culprit lesions in ACS

The importance of myocardial salvage during the acute phase of infarction is emphasised by the fact that prognosis is driven largely by ultimate infarct size. We could therefore hypothesise that treating all significant lesions is beneficial. One of the first primary PCI randomised trials testing this hypothesis was reported last year. Among 214 patients with multivessel disease, adverse event rates during a mean follow-up of 2.5 years were higher with culprit-only PCI compared with multivessel PCI, whether performed during the index procedure or as a staged procedure afterwards.[73] However, the trial was small and not definitive, a more recent meta-analysis finding in favour of culprit-only primary PCI with a staged strategy for non-culprit lesions.[74] This has become the guideline recommendation and was further supported by analysis of observational data from the HORIZONS-AMI trial in which outcomes for 275 patients treated with single-procedure stenting were compared with outcomes for 393 patients treated with staged procedures.[75] The single-procedure group received significantly more stents yet had a significantly higher 12 month mortality (9.2% vs 2.3%) than the staged procedure group. The weight of evidence is now firmly in favour of culprit-only stenting during primary PCI.

Infarct size and myocardial salvage

Circadian rhythms in the onset of MI are well established, the morning hours being the period of greatest risk. Intriguingly, infarct size appears to show similar circadian variation, a retrospective analysis of 811 patients with STEMI showing that creatine kinase (CK) and troponin I curves peak between 06:00 h and noon.[76] Myocardial salvage in response to reperfusion therapy with PCI is the major strategy for limiting infarct size therapeutically and can now be quantified by cardiovascular magnetic resonance (CMR). A study of 208 patients presenting with STEMI confirmed that the extent of salvage measured by CMR is closely related to long-term prognosis, patients with a myocardial salvage index (MSI) above the median level having a lower number of adverse cardiovascular events (7 vs 26) and deaths (2 vs 12) after 18.5 months than patients with MSI below the median level.[77] Myocardial reperfusion, however, can itself exacerbate injury, by a variety of mechanisms which include interstitial haemorrhage. This can be detected by CMR and was reported in 25% of patients with STEMI treated successfully by primary PCI.[78] The presence of haemorrhage was an independent predictor of adverse remodelling, as reflected by increased left ventricular (LV) end-systolic volume at 3 months. The importance of interstitial haemorrhage as a predictor of LV remodelling was emphasised by the improvement in the area under the receiver operating characteristic curves from 0.699 to 0.826 when it was added to

sti zbog poboljšanja s 0,699 na 0,826 u području ispod ROC krivulja nakon njegovog dodavanja ejekcijskoj frakciji LV i veličini infarkta u prediktivni model. Mikrovaskularna opstrukcija nakon primarne PCI također ukazuje na remodeliranje, a prema jednom drugom istraživanju na temelju CMR ona je značajno povezana s reperfuzijski krvarenjem (r^2 = 0,87, p<0,001).[79]

Strategije zaštite od reperfuzijske ozljede ostaju prioritet istraživanja i tema nedavnog preglednog članka.[80] U jednom istraživanju ispitivan je učinak eritropoetina s obzirom na pozitivne eksperimentalne učinke kod smanjenja veličine infarkta.[81] Međutim, istraživanje je bilo negativno jer su bolesnici koji su randomizirani na terapiju eritropoetinom (50.000 IU) prije primarne PCI imali veći postotak mikrovaskularne opstrukcije i dilatacije LV bez smanjenja veličine infarkta, u usporedbi s bolesnicima koji su randomizirani na terapiju placebom. Drugo istraživanje primjenilo je pletizmografiju na podlaktici za testiranje antagonista receptora bradikinina B2, polazeći od hipoteze da je endogeni bradikinin posrednik kod reperfuzijske ozljede.[82] Utvrđeno je da da je udaljeno ishemijsko prekondicioniranje spriječilo o endotelu ovisno oštećenje vazomotorne funkcije koje je bilo inducirano pletizmografijom, no blokada receptora bradikinina nije bila učinkovita. Ipak, nalaz da su podražaji koji uvjetuju klinički primjenjivo sredstvo zaštite od referfuzijske ozljede nije nešto novo, već je ponovljeno u drugim novijim kliničkim ispitivanjima. Komparativno istraživanje primarne PCI vezano za postkondicioniranje isprekidanom reperfuzijom naspram nagle reperfuzije utvrdilo je da isprekidana metoda bolje štiti mikrovaskularnu funkciju i veličinu LV nakon 12 mjeseci.[83] Isprekidana reperfuzija se pokazala također djelomično učinkovitom u jednom drugom istraživanju primarne PCI u kojem su bolesnici randomizirani na isprekidanu reperfuziju naspram kontrolnoj skupini. Nije bilo utjecaja na veličinu infarkta, osim kod bolesnika s velikim rizičnim područjem, kod kojih je postkondiciranje bilo znatno smanjeno.[84]

Korisnost intra-aortne balonske kontrapulsacije (IABC) u slučajevima kad je akutni MI kompliciran kardiogenim šokom općenito je prihvaćena. U novijem randomiziranom ispitivanju provedenom na 337 bolesnika, testirana je uloga IABC u smanjenju veličine infarkta kod hemodinamski stabilnih bolesnika s infarktom prednje stijenke miokarda.[85] Veličina infarkta u prvih 3-5 dana mjerena MRI nije pokazivala značajne razlike po skupinama, no oni bolesnici koji su bili randomizirani na IABC bili su skloniji vaskularnim komplikacijama. Autori su zaključili da IABC nema nikakvu kliničku korist za tu skupinu bolesnika.

Kontrastom uzrokovano akutno oštećenje bubrega

Nije jasno imaju li nova kontrastna sredstva, kao primjerice izoosmolarni kontrast, utjecaj na rizik od razvoja kontrastom uzrokovanog akutnog oštećenja bubrega (CI-AKI).[86] Rizik od CI-AKI je osobito visok kod bolesnika s ACS, a noviji podaci potvrđuju da značajno utječe na kliničke ishode, uključujući duljinu hospitalizacije i smrtnost.[87,88] Kod bolesnika sa ACS malo je vremena za primjenu mjera zaštite bubrežne funkcije, a mjere koje zahtijevaju do 12 sati prethodne hidracije su jasno nepraktične Potrebu za promjenom u praksi naglasili su *Wi i sur.*,[87] koji su zaključili da bi bubrežnu funkciju trebalo mjeriti bazalno, prije postupka te nakon primarne PCI radi bolje stratifikacije rizika. U međuvremenu bi pažnju trebalo posvetiti zaštiti funkcije bubrega pomoću bikarbonata, koji je prema nekim rezultatima učinkovitiji od uobičajene fiziološke otopine koja se primjenjuje kratkom infuzijom ili protokolom jednokratnog bolusa.[89] U nekim podskupinama, kao primjerice kod bolesnika koji trebaju hitnu operaciju radi infekLV ejection fraction and infarct size in the predictive model. Microvascular obstruction after primary PCI is also predictive of remodelling, and in another CMR study was found to correlate significantly with reperfusion haemorhage (r^2 = 0.87, p<0.001).[79]

Strategies to protect against reperfusion injury remain high on the research agenda and have been the subject of recent review.[80] In one study the effect of erythropoietin was tested based on beneficial experimental effects for reducing infarct size.[81] However, the study was negative, with patients randomised to erythropoietin (50 000 IU) before primary PCI showing an increased incidence of microvascular obstruction and LV dilatation without reduction in infarct size compared with patients randomised to placebo. Another study using forearm plethysmography tested a bradykinin B2 receptor antagonist, based on the hypothesis that endogenous bradykinin is a mediator of reperfusion injury.[82] The investigators found that remote ischaemic preconditioning abolished the impairment of endothelium-dependent vasomotor function induced by plethysmography, but bradykinin receptor blockade had no effect. Nevertheless, the finding that conditioning stimuli provide a clinically applicable means of protection against reperfusion injury was not new and has been replicated in other more recent clinical trials. A comparative primary PCI study of post-conditioning by staccato reversus abrupt reperfusion, for example, showed that the staccato protocol was associated with better preservation of microvascular function and LV dimensions 12 months later.[83] Staccato reperfusion was also partially effective in another primary PCI study in which patients were randomised to staccato reperfusion versus control. Infarct size was unaffected, except in patients with large areas at risk in whom it was significantly reduced by post-conditioning.[84]

The benefits of intra-aortic balloon counterpulsation (IABC) when cardiogenic shock complicates acute MI are generally accepted. Recently, the role of IABC for reducing infarct size in haemodynamically stable patients with anterior MI was tested in a randomised trial of 337 patients.[85] Infarct size at 3-5 days determined by MRI showed no significant difference between the groups, but those patients randomised to IABC showed a trend towards more vascular complications. The authors concluded that IABC produces no clinical benefit in this group of patients.

Contrast-induced acute kidney injury (CI-AKI)

Whether newer contrast agents, such as iso-osmolar contrast, have an impact on the CI-AKI risk is controversial.[86] Risk of CI- AKI is particularly high in patients presenting with an ACS, and recent data confirm it has a significant impact on clinical outcomes, including length of hospital stay and mortality.[87,88] The ACS setting offers little time to apply reno-protective measures, and strategies requiring up to 12 h of prehydration are clearly impractical. The need for a change in practice was emphasised by *Wi et al*,[87] who concluded that renal function should be measured at baseline and after primary PCI, to refine risk stratification. Meanwhile consideration should be given to reno-protection with bicarbonate, which has been reported to be more effective than normal saline using short-infusion or singlebolus protocols.[89] In certain subgroups, such as patients requiring urgent surgery for infective endocarditis, preoperative coronary angiography does not appear to increase the risk of acute kidney injury,[90] but, in general, contrast exposure should be kept at as low a level as possible during primary PCI. Meanwhile, ran-

tivnog endokarditisa, čini se da preoperativna koronarna agiografija ne povećava rizik od akutnog oštećenja bubrega,[90] iako općenito, izlaganje kontrastu bi trebalo biti što je kraće moguće tijekom primarne PCI. U međuvremenu su potrebna randomizirana ispitivanja koja bi testirala protokol kratkotrajne hidracije prije postupka ili bolus primjene potencijalno renoprotektivnih lijekova.

Stenoza karotidne arterije — je li ugradnja stenta još uvijek opcija?

Prilagodba životnog stila i lijekovi za sekundarnu prevenciju nisu uvijek učinkoviti u zaštiti od pogoršanja ateroskleroze karotidnih arterija. Nedavno ispitivanje redukcije tjelesne težine rimonabantom pokazalo je da 5% smanjenja tjelesne težine tijekom 30 mjeseci nije imalo utjecaj na pogoršanje karotidne bolesti u usporedbi s bolesnicima na placebu.[91] Kod mnogih bolesnika je stoga potrebna intervencija kod bolesti karotidnih arterija, no ostaje sporno treba li ona biti kirurška ili perkutana.[92] Veliko randomizirano ispitivanje provedeno na 2.502 bolesnika kod kojih su prisutni ili ne postoje simptomi karotidne stenoze nije pokazalo nikakvu značajnu razliku u primarnim zajedničkim ishodima (periproceduralni moždani udar, MI ili smrt ili bilo kakav ipsilateralni moždani udar unutar 4 godine) niti ikakvu razliku u učinkovitosti liječenja ovisno o tome da li je bolest bila praćena simptomima.[93] Međutim, novija meta-analiza koja se temelji na podacima iz 11 randomiziranih ispitivanja koja su uspoređivala karotidnu endarterektomiju (CEA) s ugradnjom stenta u karotidnu arteriju (CAS) pokazuju da je periproceduralni rizik od smrti ili moždanog udara niži kod CEA (OR 0,67, 95% CI 0,47 do 0,95), uglavnom zbog nižeg rizika od manjeg moždanog udara, dok su rizici od smrti ili od moždanog udara s invaliditetom bili slični u dvjema skupinama. Izgledi za periproceduralni MI ili ozljedu kranijalnog živca su znatno veći u skupini s CEA.[94] Sadašnje NICE smjernice prepoznaju CAS kao opciju liječenja bolesnika koji imaju simptomatsku stenozu karotidne arterije, no naglašavaju da bolesnici moraju biti upoznati s rizikom od moždanog udara i drugim komplikacijama povezanim s tim zahvatom. Multidisciplinarni tim bi trebao vršiti izbor bolesnika.[95]

Situacija je još manje jasna kod bolesti karotidne arterije bez simptoma. Znamo da bolesnici s karotidnom stenozom podvrgnuti operaciji srca zbog KBS imaju veći rizik od periproceduralnog moždanog udara i vjerojatno bi za njih trebalo razmotriti liječenje čak i ako nemaju simptome. Američke smjernice preporučaju CEA ako je stenoza ≥80%, bilo prije ili u kombinaciji s CABG. CAS prije CABG je alternativna opcija s dobrim rezultatima kod bolesnika za koje se smatra da su visoko rizični za CEA.[96] Pokušaji da se poboljša predviđanje rizika kod takvih bolesnika predmet su brojnih istraživanja, a nova studija s ultrazvukom karotidnih arterija navodi da su ukupna površina plaka (HR 1,29, 95% CI 1,08 do 1,55), broj plakova (HR 1,14, 95% CI 1,02 do 1,27) i broj segmenata s plakom (HR 1,45, 95% CI 1,09 do 1,93) značajno povezani s petogodišnjim rizikom od cerebrovaskularnih događaja.[97]

Transkateterska implantacija aortnog zalistka

Transkateterska implantacija aortnog zaliska (TAVI) kod starijih, visoko rizičnih bolesnika dala je odlične rezultate u većini centara, a dvogodišnje praćenje bolesnika u studiji *PARTNER* podržalo je zahvat kao alternativu operaciji kod visokorizičnih bolesnika.[98] Tako je poboljšanje površine zalistka bilo slično kod TAVI i kod operacije, a udio smrtnosti i moždanog udara tijekom praćenja bili su slični. Međutim, paravalvularna regurgitacija bila je češća nakon TAVI i imala je

domised trials testing short-duration prehydration protocols or bolus applications of potentially reno-protective substances are needed.

Carotid artery stenosis — is stenting still an option?

Life style adjustment and secondary prevention drugs may not always be effective in protecting against progression of carotid atherosclerosis. A recent trial of weight reduction with rimonabant, for example, reported that a 5% reduction in body weight over 30 months failed to influence the progression of carotid disease compared with patients who received placebo.[91] Many patients therefore require an interventional solution to their carotid disease, but whether this should be surgical or percutaneous remains contentious.[92] A large randomised trial of 2,502 patients with symptomatic or asymptomatic carotid stenosis showed no significant difference in the estimated rates of the primary composite end point (periprocedural stroke, MI, or death or any ipsilateral stroke within 4 years) and no differential treatment effect by symptomatic status.[93] However, a recent meta-analysis pooling data from 11 randomised trials comparing carotid endarterectomy (CEA) with carotid artery stenting (CAS) showed that the periprocedural risk of mortality or stroke was lower for CEA (OR 0.67, 95% CI 0.47 to 0.95), mainly driven by a decreased risk of minor stroke, whereas the risk of death or disabling stroke was similar between the two groups. The odds of periprocedural MI or cranial nerve injury were significantly higher in the CEA group.[94] Current NICE guidelines recognise CAS as a treatment option for patients with symptomatic carotid artery stenosis, but emphasise that patients need to understand the risk of stroke and other complications associated with this procedure. Patient selection should be carried out by a multidisciplinary team.[95]

For asymptomatic carotid artery disease, the situation is even less clear. We know that patients with carotid stenosis undergoing cardiac surgery for their coronary artery disease have an increased periprocedural stroke risk and probably should be considered for treatment even if asymptomatic. The American guidelines recommend CEA if the stenosis is ≥80%, either before or combined with CABG. CAS before CABG is an alternative option with good results in patients who are considered 'high risk' for CEA.[96] Attempts to refine risk prediction in such patients have been the subject of considerable research, a recent carotid ultrasound study reporting that the total plaque area (HR 1.29, 95% CI 1.08 to 1.55), the number of plaques (HR 1.14, 95% CI 1.02 to 1.27) and the number of segments with plaque (HR 1.45, 95% CI 1.09 to 1.93) were all significantly associated with the 5-year risk of cerebrovascular events.[97]

Transcatheter aortic valve implantation

Transcatheter aortic valve implantation (TAVI) in older high-risk patients has yielded excellent results in most centres, the 2-year follow-up of patients in the PARTNER trial supporting the procedure as an alternative to surgery in high-risk patients.[98] Thus improvement in valve areas was similar for TAVI and for surgery, with comparable rates of death and stroke during follow-up. However, paravalvular regurgitation was more common after TAVI and has been associated with significantly worse outcomes, the German registry reporting higher in-hospital mortality, even after multivariate adjustments for potential confounders (OR 2.50, 95% CI 1.37 to

znatno lošije ishode, a prema njemačkom registru bolnička smrtnost je bila viša, čak i nakon multivarijatne prilagodbe (OR 2,50, 95% CI 1,37 do 4,55).[99] Drugi razlog za zabrinutost je moguća ozljeda miokarda tijekom TAVI, o čemu svjedoči porast vrijednosti CK-MB u 77% od 101 bolesnika podvrgnutih nekompliciranim zahvatima.[100] Srednje maksimalne vrijednosti CK-MB bile su veće kod transapikalnog nego kod transfemoralnog pristupa (22,6 μl naspram 9,9 μl), no na njih nije utjecalo postojanje KBS. Također je primjećen i porast troponina T, što je bilo prediktivno za kardijalnu smrtnost unutar 9 mjeseci. Stoga je očito da se TAVI, kao i operativni zahvat, obično uzrokuje određeni stupanj oštećenja miokarda, što nije benigno. Međutim, u većini drugih aspekata TAVI se pokazao sigurnim i donosi dobrobit mjerljivu nestankom simptoma, kao što se vidi iz poboljšanja kvalitete života u zdravstvenom smislu, o čemu su izvjestili istraživači studije PARTNER.[101] Manja istraživanja su potkrijepila te nalaze, zabilježivši poboljšanja u vrijednostima udaljenosti tijekom 6-minutnog hoda i u kvaliteti života, a razine moždanog natriuretskog peptida (BNP) su znatno smanjene.[102] Ako se tome dodaju američke i britanske analize troškovne učinkovitosti TAVI, čini se da će se indikacije kontinuirano proširivati.[103,104] TAVI se uobičajeno primjenjuje i izvan preporučene indikacije, a dobiveni ishodi su slični onima kod zahvata s preporučenom indikacijom.[105] Paradoksalno je što se čini da veća upotreba TAVI dovodi do znatnog povećanja broja bolesnika upućenih na kiruršku zamjenu aortnog zaliska,[106] tako da, na primjer, Manchester bilježi 37% povećanja kirurške zamjene aortnog zaliska (AVR) tijekom prve 2 godine nakon početka TAVI programa.[107]

Perkutana korekcija mitralnog zalistka

Razvoj perkutanih sistema za korekciju mitralnog zaliska kod bolesnika koji pate od teškog oblika mitralne regurgitacije pokazao se izazovnijim od TAVI. NICE je 2010. godine dao opreznu ocjenu u vezi s uređajem MitraClip, preporučivši njegovo korištenje samo uz "posebne dogovore oko kliničkog liječenja, pristanak i ispitivanje bolesnika čije je stanje dovoljno dobro za kiruršku korekciju listića mitralnog zaliska".[108] Ovo se temeljilo na nalazima studije *Endovascular Valve Edge-to-Edge REpair Study* (EVEREST), opservacijskog istraživanja koje je obuhvatilo 107 bolesnika sa srednjom ili teškom mitralnom regurgitacijom, kojim je utvrđeno da je MitraClip uspješno implantiran kod 74% bolesnika, od kojih je 66% izbjeglo smrtni ishod, operaciju mitralnog zaliska i teški oblik mitralne regurgitacije (≥3+).[109] Od tada su istraživači studije EVEREST proveli daljnju opservacijsku studiju koja je uključila 78 starijih pacijenata kod kojih je konvencionalna operacija bila visokorizična, a dokazano je da uređaj *MitraClip* smanjuje mitralnu regurgitaciju kod većine bolesnika, uz smanjenje simptoma povezanih sa značajnim negativnim remodeliranjem lijeve klijetke tijekom 12 mjeseci.[110] Čini se da je korisnost *MitraClipa* usko povezana s njegovom učinkovitošću u smanjivanju mitralne regurgitacije, a srednjoročni ishodi ukazuju na znatnu povezanost s akutnim hemodinamskim odgovorom.[111]

Septalna ablacija alkoholom kod hipertrofijske kardiomiopatije

Tri istraživanja nedavno su utvrdila dugoročne ishode nakon septalnih ablacija alkoholom kod bolesnika koji imaju simptome hipertrofijske kardiomiopatije (HCM). Rezultati su bili ohrabrujući. Prema američkoj studiji, od 874 bolesnika sa simptomima NYHA III. ili IV. stupnja, šest (0,7%) ih je umrlo

4.55).[99] Another cause for concern is the potential for myocardial injury during TAVI, as evidenced by elevations of CK-MB in 77% of 101 patients undergoing uncomplicated procedures.[100] Median maximal CK-MB levels were higher for transapical than transfemoral access (22.6 μl vs 9.9 μl), but were unaffected by the presence of coronary artery disease. Elevations of cardiac troponin T were also observed and were predictive of cardiac death at 9 months. Clearly, therefore, TAVI, like surgery, is commonly associated with some degree of myocardial injury that is not benign. In most other respects, however, TAVI appears safe and has been associated with important symptomatic benefits, as reflected in the improvement in health-related quality of life reported by the PARTNER investigators.[101] Smaller studies have reinforced these findings by reporting improvement in the 6 min walk distance and quality of life scores, while brain natriuretic peptide (BNP) levels decline substantially.[102] Add to this the cost-effectiveness of TAVI in US and UK analyses, and it seems certain that indications will continue to expand.[103,104] Indeed, off-label TAVI is common-place, with reported outcomes that are comparable to on-label procedures.[105] Paradoxically, increasing TAVI activity appears to have led to a significant increase in referrals for surgical aortic valve replacement,[106] with Manchester, for example, seeing a 37% increase in surgical AVR activity within the 2 years of starting a TAVI programme.[107]

Percutaneous mitral valve repair

The development of percutaneous systems for mitral valve repair in patients with severe mitral regurgitation has proved more challenging than TAVI. NICE gave a guarded verdict on the MitraClip device in 2010, recommending it only be used with 'special arrangements for clinical governance, consent and research for patients who are well enough for surgical mitral valve leaflet repair'.[108] This was based on the findings of the Endovascular Valve Edge-to-Edge REpair Study (EVEREST) investigators in an observational study of 107 patients with moderate or severe mitral regurgitation, which reported a successful MitraClip implant in 74% of patients, of whom 66% achieved freedom from death, mitral valve surgery and severe mitral regurgitation (≥3+).[109] Since then the EVEREST investigators have undertaken a further observational study in 78 older patients at high risk of conventional surgery, which showed that the *MitraClip* device reduced mitral regurgitation in the majority of patients, with improvement in symptoms associated with significant LV reverse remodelling over 12 months.[110] The benefits of the *MitraClip* appear closely related to its efficacy in reducing mitral regurgitation, the midterm outcomes showing significant association with the acute haemodynamic response.[111]

Alcohol septal ablation in hypertrophic cardiomyopathy

Three studies have recently reported longer-term outcomes after alcohol septal ablation in symptomatic patients with hypertrophic cardiomyopathy (HCM). The results have been encouraging. Among 874 patients with class III or IV symptoms in a US study, six (0.7%) died in relation to the procedure, and survival estimates at 1, 5 and 9 years were 97%, 86% and 74%, respectively.[112] Symptoms improved to class I or II in all but 5% of cases, although 13% required repeat ablation and 3% required surgical myomectomy. In a Canadian study of 649 patients with HCM, 38% were managed conservatively, and 62% underwent invasive therapy with

uslijed zahvata, a procijenjeno preživljavanje u razdoblju od 1, 5 i 9 godina bilo je 97%, 86% i 74%.[112] Simptomi su se smanjili u NYHA I. ili II. stupanj kod svih, osim u 5% pacijenata, iako je kod 13% pacijenata bila potrebna ponovna ablacija, a kod 3% bolesnika bila je potrebna kirurška miomektomija. U kanadskom istraživanju provedenom kod 649 bolesnika s HCM, 38% bolesnika je liječeno na konzervativni način, a 62% bolesnika je podvrgnuto invazivnoj terapiji sa septalnom albacijom alkoholom (21%), kirurškom miomektomijom (71%) ili ugradnjom dvokomornog srčanog elektrostimulatora (8%).[113] U multivarijatnoj analizi invazivna terapija se nezavisno povezuje s boljim ukupnim preživljavanjem (HR 0,6; 95% CI 0,4- 0,97, p=0,04), no ne i s preživljavanjem vezanim za HCM. U invazivnoj skupini, bolesnici kojima je ugrađen elektrostimulator srca prošli su lošije nego bolesnici podvrgnuti septalnoj ablaciji ili miomektomiji, što dovodi u pitanje zahtjev za ocjenom terapije elektrostimulatorom srca u nedavnom španjolskom istraživanju koje je pokazalo pozitivne dugoročne rezultate u skupini od 50 bolesnika.[114] Na kraju, skandinavsko istraživanje zabilježilo je značajno smanjenje gradijenta u izlaznom traktu uslijed 313 ablacija provedenih kod 279 bolesnika s HCM, od kojih ih je 94% imalo simptome NYHA III/IV. stupnja.[115] Samo 21% bolesnika imalo je simptome NYHA II/IV. stupnja tijekom prve godine, s vrlo malim promjenama nakon toga. Procijenjena preživljavanja za razdoblje od 1, 5 i 10 godina iznosila su 97%, 87% i 67%, što je bilo slično preživljavanju za populacije identičnog godišta i spola. Ukupno gledajući ova istraživanja potvrđuju dugoročnu korisnost septalnih ablacija alkoholom kod HCM, što se čini valjanom alternativom operaciji kod HCM sa izraženim simptomima koja ne reagira na farmakološku terapiju.

alcohol septal ablation (21%), surgical myomectomy (71%) or dual chamber pacing (8%).[113] In multivariate analysis, invasive therapy was independently associated with better overall survival (HR 0.6; 95% CI 0.4 to 0.97, p=0.04), but not with HCM-related survival. Among the invasive group, the pacemaker-treated group fared less well than patients treated with septal ablation or myomectomy, questioning the call for a reappraisal of pacemaker therapy in a recent Spanish study that reported favourable long-term results in a group of 50 patients.[114] Finally, a Scandinavian study reported marked reductions in outflow tract gradients in response to 313 ablation procedures in 279 patients with HCM, of whom 94% had class III/IV symptoms.[115] Only 21% had class II/IV symptoms at 1 year, with little change thereafter. Estimated survival rates at 1, 5 and 10 years were 97%, 87% and 67%, respectively, and were comparable to survival rates in an age- and gender- matched population. Taken together, these studies testify to the long-term benefits of alcohol septal ablation in HCM, which appears to be a valid alternative to surgery in symptomatic HCM that does not respond to medical therapy.

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