Pregledni članak Review paper

Almanah 2011. godine: stabilna koronarna bolest.

Časopisi nacionalnih društava predstavljaju odabrana istraživanja koja predstavljaju napredak u kliničkoj kardiologiji

Almanac 2011: stable coronary artery disease.

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

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Stabilna angina pektoris

Dijagnostička strategija

Rasprostranjeni program specijalističkih klinika za ranu procjenu pacijenata s bolovima u prsištu se fokusirao na učinkovitost dijagnostičkog testiranja. U studiji na oko 400.000 pacijenata sa sumnjom na koronarnu bolest srca (KBS), dijagnostički doprinos kateterizacije srca je bio svega 37,6%, što dovodi do potrebe za boljim strategijama stratifikacije rizika.[1] Kao što je istaknuto u diskusiji, spomenuti manji doprinos pretrage vjerojatno je uzrokovana pristranošću metode, što je posljedica upućivanja pacijenata s niskim rizikom temeljem rezultata neinvazivnih testova, poput ergometrijskog testiranja.[2] Slična razmatranja su potakla NICE skupinu za smjernice da preporuči selektivniji pristup neinvazivnom testiranju temeljen na pažljivoj kliničkoj procjeni vjerojatnosti bolesti kod pacijenta koji imaju stabilne bolove u prsištu.[3] Za one s jasnim anamnestičkim podacima u krajnjim granicama dijagnostičke vjerojatnosti (<10% ili >90%) dijagnostički testovi nisu smatrani potrebnima, dok se za pacijente s visokom vjerojatnosti bolesti (60-90%) preporučala invazivna angiografija bez prethodnog testiranja na ishemiju. Zahtjev NICE za mjerenje kalcifikacija koronarnih arterija kompjutoriziranom tomografijom (*calcium scoring*) kod pacijenata s niskom (10-30%) vjerojatnosti bolesti je stvorio najveću zabrinutost, naročito po objavi izvješća da je 19% pacijenata bez koronarnih kalcifikacija — kod kojih bi prema algoritmu NICE bila isključena angina — imalo opstruktivnu (>50% stenoza) bolest.[4] Međutim, skupina pacijenata u ovoj studiji upućena na angiografiju je imala visoku vjerojatnost bolesti već i prije testiranja, a kod populacije s nižim rizikom calcium scoring zadržava visoku dijagnostičku osjetljivost.[5] Preporuke NICE su se većinom vodile analizom troškova, no potrebno je tek vidjeti da li će poboljšati dijagnostički doprinos kateterizacije srca.

Cirkulirajući biomarkeri kod stabilne angine

Klinička uloga cirkulirajućih biomarkera u dijagnozi opstruktivne KBS kod pacijenata sa sumnjom na anginu još

Stable angina pectoris

Diagnostic strategies

The widespread application of specialist clinics for early evaluation of patients with chest pain has focused attention on the effectiveness of diagnostic testing. In a study of nearly 400,000 patients with suspected coronary artery disease (CAD), the diagnostic yield of cardiac catheterisation was only 37.6%, leading to calls for better strategies for risk stratification.[1] As pointed out in correspondence, the low yield was probably due to verification bias, itself a consequence of basing referral decisions in low-risk populations on non-invasive tests such as exercise ECG.[2] Similar considerations prompted the NICE guideline group to recommend a more selective approach to non-invasive testing based on a careful clinical assessment of disease probability in patients presenting with stable chest pain.[3] For those, with unequivocal histories at the extremes of diagnostic probability (<10% or >90%) no diagnostic tests were considered necessary, while for patients with a high probability of disease (60-90%) invasive angiography without prior ischaemia testing was recommended. The NICE call for CT calcium scoring in patients with a low (10-30%) probability of disease generated greatest concern, particularly after a report that 19% of patients without coronary calcification — who would have been ruled out for angina in the NICE algorithm — had obstructive (>50% stenosis) disease.[4] However, the population referred for angiography in this study had a high pre-test probability of disease and in lower-risk populations CT calcium scoring retains a high diagnostic sensitivity.[5] NICE recommendations were driven largely by cost-effectiveness analysis but whether they will improve the diagnostic yield of cardiac catheterisation remains to be seen.

Circulating biomarkers in stable angina

The clinical role of circulating biomarkers for diagnosis of obstructive CAD in patients with suspected angina

nije definirana. U jednoj od studija, analizirana je vrijednost NT-proBNP i različitih upalnih markera kod 243 pacijenata. Samo se vrijednost NT-proBNP pokazala od značajne dijagnostičke koristi, s graničnom koncentracijom <25 ng/l koja predviđa normalan rezultat perfuzijske scintigrafije s negativnom prediktivnom vrijednosti >95%.[6] Slično, u angiografskoj studiji 848 muškaraca i žena s kliničkom sumnjom na KBS, NT-proBNP se pokazao boljim od visoko-osjetljivog C-reaktivnog proteina (hsCRP) i γ-glutamiltransferaze, pokazujući značajnu povezanost s trožilnom KBS, no nije dodao prediktivnu vrijednost tradicionalnim čimbenicima kardiovaskularnog rizika. Autori su stoga morali zaključiti da je, kao dijagnostički alat, ograničene dodatne vrijednosti.[7] Prognostička primjena cirkulirajućih biomarkera u stabilnoj KBS je također bila razočaravajuća. U meta-analizi 83 prospektivne studije koje su izvijestile o povezanosti CRP sa smrti i ne-fatalnim kardiovaskularnim epizodama, autori su zaključili da je kvaliteta studija toliko loša (samo dvije su izvijestile o mjeri diskriminacije), uz dokaze o pristranosti izvještavanja i pristranosti publikacija, da ih nisu mogli preporučiti kliničku praksu.[8] No ipak, podaci nam ukazuju da je malo vjerojatno da će mjerenje CRP dodati bilo što prognostičkoj diskriminaciji ostvarenoj mjerenjem arterijskog tlaka i ostalih kliničkih čimbenika u ovoj skupini pacijenata. U drugoj studiji je zaključeno da konvencionalni klinički podaci predstavljaju učinkovito sredstvo stratifikacije rizika kod pacijenata sa stabilnom KBS koji čekaju operacijski zahvat ugradnje aortokoronarne premosnice (CABG) te je mala vjerojatnost da će se dodatni prognostički podaci od mjerenja vrijednosti CRP, pojedinačno ili u kombinaciji s ostalim biomarkerima, pokazati učinkovitima.[9]

Farmakološko liječenje angine

Farmakološko liječenje angine predstavlja temu od ponovnog interesa, kako zbog dostupnosti novih lijekova (ivabradin i ranolazin), tako i zbog dokaza da se kod mnogih pacijenata može uspoređivati s rezultacijama revaskularizacije ne samo za kontrolu simptoma nego i poboljšanje prognoze. Studija COURAGE je dokazala da kod pacijenata koji su liječeni tzv. optimalnom farmakološkom terapijom (acetilsalicilna kiselina, beta-blokator i statin, uz ACE inhibitor prema indikaciji), liječenje perkutanom koronarnom intervencijom (PCI) ne poboljšava kardiovaskularne ishode, a dobrobiti u kvaliteti života nestaju tijekom 36 mjeseci.[10,11] Novije meta-analize studija koje su randomizirale pacijente sa stabilnom anginom na PCI ili farmakološko liječenje su došle do sličnih zaključaka.[12,13] Ovo je potaklo skupine za smjernice da preporuče optimalno farmakološko liječenje za početno zbrinjavanje stabilne angine, dok je revaskularizacija rezervirana, prije svega, za pacijente čiji simptomi nisu zadovoljavajuće kontrolirani.[14]

Prognoza angine

Od ranih otkrića Framinghamske studije da angina ima "mortalitet iznenađujuće sličan onome koji slijedi nakon bolničkog liječenja infarkta miokarda"[15] do tvrdnji ispitivača da se "kardiovaskularni rizik pomoću moderne terapije smanjuje na normalnu razinu",[16] čini se da smo sada prošli puni krug s dvije nedavne studije ishoda za pacijente s anginom. Prva je uključivala 1.609 odraslih osoba s ishemijskom bolesti srca (IBS) koje su identificirane u primarnoj zdravstvenoj skrbi te stoga nisu bile podložne pristranosti

has yet to be defined. In one study, blood samples for the N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) and various inflammatory markers were obtained in 243 patients before myocardial perfusion imaging. Only NT-proBNP proved significantly diagnostic, a cut-off concentration <25ng/l predicting a normal perfusion scan with a negative predictive value >95%.[6] Similarly, in an angiographic study of 848 men and women with clinically suspected CAD, NT-proBNP performed better than high-sensitivity C-reactive protein (hsCRP) and γ-glutamyltransferase, showing significant association with three-vessel CAD, but it did not add to the predictive value of traditional cardiovascular risk factors. The authors were forced to conclude that it was of limited incremental value as a diagnostic tool.[7] The prognostic application of circulating biomarkers in stable CAD has also been disappointing. In a meta-analysis of 83 prospective studies reporting the association of CRP with death and non-fatal cardiovascular events, the authors found that the quality of the studies was so poor (only two reported a measure of discrimination), with evidence of reporting bias and publication bias, that they were unable to make clinical practice recommendations.[8] Nevertheless, the data suggested that CRP measurements are unlikely to add anything to the prognostic discrimination achieved by considering blood pressure and other clinical factors in this patient group. In another study it was concluded that conventional clinical information provided an effective means of risk-stratifying patients with stable CAD awaiting coronary bypass surgery and that additional prognostic information from CRP, measured singly or in combination with other biomarkers, was unlikely to be cost-effective.[9]

Medical treatment of angina

The medical treatment of angina has been the subject of renewed interest, because of the availability of new treatments such as ivabradine and ranolazine, and also because of the recognition that it can compete favourably with revascularisation in many patients, both for controlling symptoms and for improving prognosis. Thus, COURAGE showed that in patients receiving optimal medical treatment (aspirin, β blocker and statin, plus ACE inhibitor as indicated), percutaneous intervention (PCI) does not improve cardiovascular outcomes and incremental benefits in quality of life disappear by 36 months.[10,11] More recent meta-analyses of trials that have randomised patients with stable angina to PCI or medical treatment have come to similar conclusions.[12,13] This has led guideline groups to recommend optimal medical treatment for the initial management of stable angina, with revascularisation reserved principally for patients whose symptoms are not satisfactorily controlled.[14]

Prognosis of angina

From the early Framingham finding that angina has 'a mortality surprisingly close to that which follows the post-hospital phase of myocardial infarction'[15] to the trialists' assertions that 'cardiovascular risk (is) reduced to normal levels with contemporary therapy',[16] we now appear to have gone full circle with two recent outcome studies for patients with angina. The first included 1,609 adults with ischaemic heart disease (IHD) who were identified in pri-

pri odabiru koja može utjecati na odabir u skupini u sekundarnoj zdravstvenoj zaštiti.[17] Ispitivači su ustanovili da rizici smrti od svih uzroka i koronarne smrti kod pacijenata s anginom u usporedbi s onima s preboljelim infarktom miokarda iznose 0,73 (95% CI 0,55 do 0,98) odnosno 0,65 (0,44 do 0,98). Iako statistički značajne na razini od p<0,05 ove razlike nisu bile značajne na razini p<0,01 koja je primjerena za opservacijska istraživanja. Istraživači su također ustanovili da je fizička kondicija kod onih koji su imali samo anginu bila niže. U drugoj studiji, ista skupina je ispitivala prognozu 1.785 pacijenata s anginom kao prvom manifestacijom IBS.[15] Unutar 5 godina, 116 (6,5%) je preživjelo akutni infarkt miokarda, a 175 (9,8%) je umrlo. Muški spol i svaka dodatna godina starosti su oboje povezani s povećanim omjerom rizika za akutni infarkt miokarda (2,01 (1,35 do 2,97) i 1,04 (1,02 do 1,06)) i ukupnom smrtnošću (1,82 (1,33 do 2,49) odnosno 1,09 (1,07 do 1,11). Značajan rezultat je taj da je akutni infarkt miokarda nakon početne epizode angine značajno povećao rizik od predstojećeg smrtnog ishoda. Autori su zaključili da bi se kod pacijenata s anginom koji predstavljaju visokorizičnu skupinu u primarnoj skrbi trebala agresivno provoditi odgovarajuća kontrola čimbenika rizika i optimalna uporaba preventivnog farmakološkog liječenja.

Intervencijsko liječenje stabilne koronarne bolesti srca

Klinička ispitivanja

Očekivanja da bi studija COURAGE mogla dovesti do promjena u liječenju stabilne angine, uz obnovljeni naglasak na optimalno farmakološko liječenje (OMT) kao primarnu strategiju,[19] se tek moraju ispuniti, što dovodi do pitanja koliko su pacijenti informirani o rizicima i dobrobitima PCI.[20] Ova pitanja su naglašena nedavnim studijama koje pokazuju da se PCI preporuča znatno češće nego CABG i nego što to indiciraju međunarodne smjernice, a kriteriji američkog udruženja za primjerenost ispunjeni su u svega 50,4% slučajeva.[21,22] Učestalost PCI u SAD se od objave studije COURAGE[23] ne smanjuje, a većina pacijenata se ne liječi primjenom optimalnog farmakološkog liječenja. U velikoj studiji s elektivnim PCI, udio OMT je bio svega 43,5% 19 mjeseci prije publikacije studije COURAGE te 44,7% 24 mjeseca nakon toga, što potvrđuje da COURAGE još nije imala očigledan učinak na intervencijsku praksu.[24]

Ono što se može zamijetiti u novijim izvješćima iz drugih studija s PCI su podaci 10-godišnjeg praćenja iz studije MASS II i rezultati studije STICH. U istraživanju MASS II je bilo randomizirano 611 pacijenata s anginom, višežilnom bolesti koronarnih arterija i očuvanom funkcijom lijeve klijetke (LV) na inicijalne strategije farmakološkog liječenja ili PCI ili CABG.[25] Studija nije imala adekvatnu snagu jer je imala malo primarnih ishoda (ukupni mortalitet, infarkt miokarda s Q-zupcem, ili refraktorna angina s potrebom revaskularizacijom), koji su se pojavili rjeđe u skupini liječenoj pomoću CABG nego u skupini liječenoj PCI i skupini s farmakološkim liječenjem (33%, 42% i 59%). U studiju MASS II nisu bili uključeni pacijenti sa značajnom bolesti glavnog debla lijeve koronarne arterije, a ukupna smrtnost je bio slična u sve tri skupine. No ipak, rezultati su bili slični onima iz ranijih randomiziranih studija gdje su uspoređeni CABG naspram farmakološkog li-

mary care and were not, therefore, prone to the selection bias that affects secondary care cohorts.[17] The investigators found the hazards of all-cause and coronary death in patients with angina alone compared with patients who had had previous myocardial infarction (MI) were 0.73 (95% CI 0.55 to 0.98) and 0.65 (0.44 to 0.98), respectively. Although statistically significant at the p<0.05 level these differences were not significant at the p<0.01 level suggested as appropriate for observational research. The investigators also found that physical functioning was consistently lower among those with angina alone. In the second study, the same group examined the prognosis of 1,785 patients with angina as a first manifestation of IHD.[18] Within 5 years, 116 (6.5%) had an acute MI, and 175 (9.8%) died. Male sex and each year of increasing age were both associated with increased HRs for acute MI (2.01 (1.35 to 2.97) and 1.04 (1.02 to 1.06), respectively) and all-cause mortality (1.82 (1.33 to 2.49) and 1.09 (1.07 to 1.11), respectively). An important finding was that an acute MI after the index episode of angina greatly increased the risk of subsequent death. The authors concluded that appropriate control of risk factors and optimal use of preventive medical treatments should be aggressively pursued in patients with angina who represent a high-risk group in primary care.

Interventional management of stable coronary artery disease

Clinical trials

Expectations that COURAGE would lead to changes in the management of stable angina, with renewed emphasis on optimal medical treatment (OMT) as the primary strategy,[19] have yet to be fulfilled, raising questions about how well informed patients are about the risks and benefits of PCI.[20] These questions have been amplified by recent studies showing that PCI is recommended rather than coronary artery bypass grafting (CABG) substantially more often than indicated by international guidelines, and fulfils the US societies' criteria for appropriateness in only 50.4% of cases.[21,22] Rates of PCI in the USA have shown no tendency to decline since the publication of COURAGE[23] and a majority of patients are not being treated with OMT. In a large study of elective PCI procedures, rates of OMT were only 43.5% in the 19 months before publication of COURAGE and 44.7%, in the 24 months afterwards, confirming that COURAGE has not yet had a palpable effect on interventional practice.[24]

Notable among recent reports from other PCI trials are the 10-year follow-up data from MASS II and the results of the STICH trial. MASS II randomised 611 patients with angina, multivessel CAD and preserved left ventricular (LV) function to initial strategies of medical treatment or PCI or CABG.[25] The study was underpowered for the primary end point of total mortality, Q-wave MI, or refractory angina needing revascularisation, which occurred less frequently in the CABG group than in the PCI and medical treatment groups (33%, 42% and 59%, respectively). MASS II excluded patients with significant left main stem disease, and total mortality was similar in all three groups. Nevertheless, the findings bear comparison with those reported in the early randomised trials of CABG versus medical treatment[26]

ječenja[26] gdje su pacijenti s višežilnom koronarnom bolesti randomizirani na CABG preživjeli dulje od onih randomiziranih na farmakološko liječenje.

Studija STICH je također potaknula određene sumnje o vrijednosti dotadašnjih randomiziranih studija. U studiji STICH 1.212 pacijenata s višežilnom bolesti i teškim oštećenjem funkcije lijeve klijetke (ejekcijska frakcija <35%) bilo je randomizirano na CABG ili farmakološko liječenje, kako bi se testiralo da li kirurška revaskularizacije poboljšava preživljavanje u ovoj visoko-rizičnoj skupini s ishemijskom disfunkcijom lijeve klijetke.[27] Nakon gotovo 5 godina praćenja svi uzroci smrtnosti (primarni ishod) je bio sličan u obje skupine te i glavna studijska skupina i podskupina su pokazale vijabilnost miokarda.[28] Rezultati studije STICH potvrđuju ranije rezultate[29] da su dobrobiti revaskularizacije kod pacijenata s ishemijskom kardiomiopatijom preuveličane, čak i kod pacijenata s dokazivom vijabilnosti. Kao što je urednik komentirao, učinak modernog farmakološkog liječenja se ne bi trebalo podcijeniti u zbrinjavanju teškog oblika KBS.[30]

Daljnje studije koje su uspoređivale PCI naspram CABG u odabranim skupinama pacijenata s bolesti glavnog debla lijeve koronarne arterije su bile dosljedne u dobrobiti CABG, isključivo na temeljem smanjene učestalosti ponovljenih revaskularizacija u usporedbi s PCI.[31-33] Niti jedna od ovih studija nije pokazala značajnu razliku u smrtnosti između dvije strategije revaskularizacije, što PCI čini opcijom za one pacijente koji se nisu voljni podvrgnuti operativnom zahvatu i spremni su prihvatiti daljnje intervencijske postupke ako bi to bilo potrebno. Studija SYNTAX je već identificirala PCI kao razumnu strategiju za simptomatsku višežilnu KBS, naročito ako je rezultat SYNTAX ljestvice nizak (≤22) kada su kardiovaskularni krajni ishodi nakon 3 godine usporedivi s onima od CABG, a to je pojačano usporednim ishodima kvalitete života.[34-36] Nedavna predspecificirana analiza podskupina iz registra ARTS-II je izvijestila o usporednim ishodima za pacijente s višežilnom bolesti koja je uključivala proksimalnu lijevu prednju silaznu koronarnu arteriju liječenu stentovima koji luče sirolimus (SES) ili CABG.[37] Ove usporedbe, PCI naspram CABG kod visokorizične bolesti te farmakološkog liječenja nasuprot CABG kod ishemijske kardiomiopatije, počele su narušavati povjerenje u dugotrajni stav da su kirurški zahvati najprimjerenija opcija za liječenje tih skupina pacijenata.

Čimbenici postupka

Usporedba radijalnog i femoralnog pristupa

RIVAL, prva komparativna studija vođena kardiovaskularnim ishodima, nije riješila debatu o prednostima radijalnog u odnosu na femoralni pristup prilikom intervencijskih postupaka.[38] Od 7.021 pacijenata s akutnim koronarnim sindromom koji su bili podvrgnuti kateterizaciji srca s ciljem intervencije, zajednički primarni ishod (smrt, infarkt miokarda, moždani udar ili krvarenje koje nije povezano s CABG unutar 30 dana) je nastupio u sličnim omjerima u skupinama s radijalnim (3,7%) i femoralnim (4,0%) pristupom. Marginalna razlika u korist radijalnog pristupa registrirana je zbog trenda manje učestalosti krvarenja unutar 30 dana (0,7% naspram 0,9%), koje su bile povezane sa znatno nižim stopama komplikacija pri lokaciji pristupa, uključujući velike hematome i pseudoaneurizme. Manje studije[39] su izvijestile o nižoj učestalosti krvarenja kod radi-

where patients with multivessel disease who were randomised to CABG survived longer than those randomised to medical treatment.

STICH also has raised some doubt about the contemporary validity of those early randomised trials. In STICH 1,212 patients with multivessel disease and severe impairment of LV function (ejection fraction <35%) were randomised to coronary artery bypass surgery or medical treatment, to test whether surgical revascularisation would improve survival in this high-risk group with ischaemic LV dysfunction.[27] After nearly 5-years' follow-up all-cause mortality (the primary end point) was similar between the groups, both in the main trial cohort and in a subgroup with demonstrable myocardial viability.[28] STICH confirms earlier reports[29] that the benefits of revascularisation in patients with ischaemic cardiomyopathy may have been exaggerated, even in patients with demonstrable viability. As the editorialist commented, contemporary medical treatment should not be underestimated in the management of severe CAD.[30]

Meanwhile, further trials of PCI versus CABG in selected groups with left main stem disease have been consistent in favouring CABG, based almost exclusively on lower rates of repeat revascularisation compared with PCI.[31-33] None of these trials showed significant mortality differences between the two revascularisation strategies, making PCI an option for those patients unwilling to undergo surgery and prepared to accept further interventional procedures as necessary. The SYNTAX trial has already identified PCI as a reasonable strategy for symptomatic multivessel disease, particularly if the SYNTAX score is low (≤22) when cardiovascular end points at 3 years are comparable to those for CABG, and this is reinforced by comparable quality-of-life outcomes.[34-36] More recently, a prespecified subgroup analysis of the ARTS-II registry has reported comparable outcomes for patients with multivessel disease involving the proximal left anterior descending coronary artery treated with either sirolimus-eluting stents (SES) or CABG.[37] These comparisons of PCI versus CABG in high-risk disease, and medical treatment versus CABG in ischaemic cardiomyopathy begin to erode confidence in the long-held view that surgery is the most appropriate treatment option in such patients.

Procedural factors

Radial versus femoral access

Debate about the merits of radial versus femoral access for interventional procedures has not been resolved by RIVAL, the first comparative study powered for cardiovascular outcomes.[38] Among 7,021 patients with acute coronary syndrome (ACS) undergoing cardiac catheterisation with a view to intervention, the primary outcome (a composite of death, myocardial infarction, stroke or non-CABG-related bleeding at 30 days) occurred in similar proportions of radial (3.7%) and femoral (4.0%) access groups. The marginal difference in favour of radial access was driven by a trend towards lower bleeding rates at 30 days (0.7% vs 0.9%), associated with significantly lower rates of access site complications, including large haematomas and pseudoaneurysms. Smaller studies[39] have reported less bleeding with radial access which, coupled with earlier mobilisation, has encouraged its adoption in many European cen-

jalnog pristupa što je, zajedno s ranijom mobilizacijom pacijenta, potaknulo njegovo usvajanje u mnogim europskim centrima. Međutim, femoralni pristup i dalje preferiraju mnogi intervencijski kardiolozi zato što je pristup predvidljiviji, vrijeme postupka može biti kraće i izlaganje zračenju niže nego kod radijalnog pristupa.[40,41] Naposljetku, čini se da je iskustvo ustanove glavna odrednica uspjeha intervencije, tako da u studiji RIVAL visokovolumni s radijalnim pristupom bilježe najnižu opasnost od zajedničkog primarnog ishoda.

"Pressure wire"

Ispitivanje koronarne cirkulacije (pressure wire) mjerenjem frakcijske rezerve protoka (FFR) uveliko koriste intervencijski kardiolozi za procjenu funkcijskog značaja koronarne stenoze prije same intervencije. U studiji FAME 1.005 pacijenata s višežilnom KBS podvrgnutih implantaciji stentova koji otpuštaju lijekove (DES) je randomizirano na postupke koji su vođeni isključivo angiografijom ili angiografijom uz mjerenje indeksa FFR, čije su vrijednosti indicirale stentiranje ako su bile <0,80.[42] U skupini FFR, broj stentova po pacijentu (1,9±1,3 nasuprot 2,7±1,2) i primarnih ishoda smrti, ne-fatalnih infarkta miokarda ili revaskularizacija ciljne žile nakon 1 godine (13,2% nasuprot 18,3%) je bio značajno niži nego u angiografskoj skupini. Dobrobit je većinom registrirana i nakon 2 godine[43], a dokazi troškovne učinkovitosti[44] upotpunjuju ove rezultata u korist PCI uz FFR kod intervencija na više krvnih žila.

Perkutana koronarna intervencija bifurkacijskih lezija

Debata koja okružuje primjenu PCI u bifurkacijskim lezijama je većinom razriješena u studijama koje su pokazale da je jednostavno stentiranje glavnog kraka — s "privremenim" stentiranjem bočnog kraka samo ako protok postane ugrožen — bolje nego strategije koje uključuju složeno stentiranje oba kraka bifurkacije. Nedavna meta-analiza randomiziranih studija je potvrdila nadmoć strategije jednostavnog stentiranja koja daje bolje rezultate za nastanak infarkta miokarda tijekom bolničkog liječenja i kasnije te sličnu učestalost restenoze i revaskularizacije ciljane žile u usporedbi sa složenom strategijom.[45] Daljnje usavršavanje jednostavne strategije stentinga je sada istraženo randomiziranjem 477 pacijenata ili na konačnu "kissing balloon" inflaciju ili bez nje.[46] Konačna "kissing balloon" inflacija je bila povezana sa značajno nižom učestalosti angiografske restenoze bočnog kraka (8% nasuprot 15%) unutar 6 mjeseci u usporedbi sa skupinom bez konačne "kissing balloon" inflacije, mada je učestalost primarnog zajedničkog ishoda (srčana smrt, infarkt miokarda, tromboza stenta ili revaskularizacija ciljne lezije) bila slična (2,1% naspram 2,5%). Stoga, podaci ne daju snažan argument za konačnu "kissing balloon" inflaciju nakon jednostavnog stentinga bifurkacije, iako se čini da strategija pruža zaštitu od restenoze bočnog kraka.

Uređaji za potporu lijevoj klijetci

Intra-aortna balonska pumpa se naširoko preporuča kao podrška kod visokorizične PCI, no nedavna randomizirana studija sa 301 pacijenata s teškom disfunkcijom lijeve klijetke (ejekcijska frakcija ≤30%) i uznapredovalom KBS nije pronašla dokaze o koristi iste.[47] Učestalost neželjenih kardioloških događaja tijekom bolničkog liječenja je bila slična s (15,2%) ili bez (16,0%) intra-aortne balonske

tres. Femoral access, however, is still preferred by many operators because access is more predictable, procedure times may be shorter and radiation exposure lower than with the radial approach.[40,41] Ultimately, it seems, institutional experience is a major determinant of procedural success, high-volume radial centres in RIVAL recording the lowest hazard of the primary outcome.

Pressure wire

Pressure wire measurement of fractional flow reserve (FFR) is now widely used by interventionists for per-procedural assessment of the functional significance of coronary stenoses. In the FAME study 1,005 patients with multivessel CAD undergoing drug-eluting stent (DES) implantation were randomised to procedures guided by angiography alone or by angiography plus FFR measurement, values <0.80 providing indication for stenting.[42] In the FFR group, the number of stents per patient (1.9±1.3 vs 2.7±1.2) and the primary end point of death, non-fatal MI or target vessel revascularisation at 1 year (13.2% vs 18.3%) were both significantly lower than for the angiography group. Benefits were largely sustained at 2 years[43] and evidence of cost-effectiveness44 completes the case in favour of FFR-guided PCI in multivessel procedures.

Bifurcation PCI

Debate surrounding bifurcation PCI has been largely resolved by studies showing that simple stenting of the main branch — with 'provisional' stenting of the side branch only if flow becomes compromised-is better than strategies that involve complex stenting of both limbs of the bifurcation. A recent meta — analysis of randomised trials has confirmed superiority of the simple stenting strategy which yields better results for in-hospital and late MI and similar rates of restenosis and target vessel revascularisation compared with the complex strategy.[45] Further refinement of the simple stenting strategy has now been tested by randomising 477 patients either to final kissing balloon inflation or to no-final kissing balloon inflation.[46] Final kissing balloon inflation was associated with a significantly lower rate of angiographic side branch restenosis (8% vs 15%) at 6 months compared with no-final kissing balloon inflation, although rates of the primary end point-cardiac death, myocardial infarction, stent thrombosis, or target-lesion revascularisation-were similar (2.1% vs 2.5%). The data, therefore, do not provide a compelling argument for final kissing balloon inflation after simple birfurcation stenting, although the strategy does seem to provide some protection against side branch restenosis.

LV support devices

Intra-aortic balloon pump support in high-risk PCI is widely recommended, but a recent randomised trial in 301 patients with severe LV dysfunction (ejection fraction ≤30%) and advanced CAD found no evidence of benefit.[47] Rates of in-hospital major adverse cardiac events were similar with (15.2%) or without (16.0%) the intra-aortic balloon pump, arguing against its elective use in this group of patients. Alternative methods of circulatory support during PCI are now being investigated and registry data for the *Impella 2.5* percutaneous LV assist device confirm that it can

pumpe, što predstavlja argument protiv njezinog elektivnog korištenja u ovoj skupini pacijenata. Sada se ispituju alternativne metode cirkulatorne potpore tijekom PCI, a podaci iz registra za uređaj za perkutanu potporu lijevoj klijetci *Impella 2.5* potvrđuju da se može sigurno pozicionirati preko aortnog zaliska iz femoralnog pristupa i dostavljati protok od do 2,5 l/min tijekom intervencijskih postupaka.[48] Ovi obećavajući podaci ističu uređaj *Impella* od većine ostalih koji zahtjevaju kirurško postavljanje te nemaju ulogu u laboratoriju za kateterizaciju.[49]

Komplikacije

Akutno bubrežno oštećenje

Kontrastom inducirano akutna oštećenje bubrega (AKI) predstavlja dobro poznatu komplikaciju angiografskih postupaka, a nedavna kanadska studija je utvrdila povezanost s neželjenim dugoročnim ishodima.[50] Kod 14.782 odraslih pacijenata podvrgnutih kateterizaciji srca, prilagođeni rizik od smrti tijekom praćenja od 19,7 mjeseci je progresivno porastao ovisno o postproceduralnoj ozbiljnosti AKI. Tako su pacijenti s AKI stupnjem 2 ili 3 tijekom prvih 7 dana nakon kateterizacije imali gotovo četiri puta veći rizik od smrti u usporedbi s pacijentima bez AKI. Rizik naknadne hospitalizacije zbog zatajivanja srca se također povisio. Zanimljivo je da je AKI rjeđe zabilježen kod kateterizacije kod koje je korišten radijalni pristup u usporedbi s femoralnim pristupom.[51] Hidratacija prije intervencije može biti korisna kod visokorizičnih osoba, naročito dijabetičara, ali niti jedan drugi postupak nije pokazao jasnu dobrobit.

Krvarenje

Periproceduralno krvarenje koje se povezuje s nepovoljnim ishodima nakon PCI se zadnjih godina značajno smanjilo.[52] Tome je najvjerojatnije najveći doprinos dao radijalni pristup (vidi gore), ali su i druge strategije izbjegavanja krvarenja naglašene u studiji na 1.522.935 pacijenata iz CathPCI registra — Nacionalnog registara kardiovaskularnih podataka.[53] Studija je pokazala da su uređaji za vaskularno zatvaranje i terapija bivalirudinom zajedno povezani sa smanjenjem epizoda krvarenja sa 2,8% na 0,9%, ali su ipak ove strategije najrjeđe korištene na pacijentima s visokim prijeproceduralnim rizikom krvarenja procijenjenim prema modelu rizika od krvarenja Nacionalnog registra kardiovaskularnih podataka.[54] Na temelju rezultata ovih nalaza se čini da ostaje značajan prostor za poboljšanje sigurnosti PCI identifikacijom pacijenata prije samog zahvata koji će imati najveću dobit od individualiziranih strategija izbjegavanja krvarenja.

Ozljeda miokarda

Ozljeda miokarda tijekom PCI je uobičajena i nedavna meta-analiza 15 studija koje su obuhvatile 7.578 pacijenata je ustanovila elevaciju troponina kod 28,7% postupaka.[55] Bilo koja razina povišenog troponina je povezana s povećanim rizikom od kardiovaskularnih epizoda i za one s infarktom miokarda prema univerzalnoj definiciji omjer šansi za glave nepovoljne kardiološke epizode nakon 18 mjeseci je iznosio 2,25 (1,26 do 4,00). Izravan dokaz periproceduralne ozljede miokarda je sada dostupan preko kardiovaskularne magnetske rezonancije, koja je dokumentirala novo hiperpovećanje mase miokarda (srednja masa 5,0 g) u 32% od 152 pacijenta podvrgnutih postupbe safely positioned across the aortic valve from the femoral approach and supply flow rates of up to 2.5 l/min during interventional procedures.[48] These promising data distinguish the *Impella* from most other LV assist devices, which require surgical deployment and have no role in the catheter laboratory.[49]

Complications

Acute kidney injury

Contrast-induced acute kidney injury (AKI) is a well-recognised complication of angiographic procedures, and a recent Canadian study shows that it has important association with adverse long-term outcomes.[50] Among 14,782 adults undergoing cardiac catheterisation, the adjusted risk of death during a median 19.7 months' follow-up increased progressively with the post-procedural severity of AKI-patients with stage 2 or 3 AKI during the first 7 days after catheterisation having nearly four times the hazard of death compared with patients with no AKI. Risks of subsequent hospitalisations for heart failure also increased. Interestingly, AKI has been reported less commonly with catheterisation using the radial approach compared with the femoral approach.[51] Pre-hydration may be protective in high-risk individuals, particularly people with diabetes, but no other specific treatments have shown unequivocal benefit.

Bleeding

Peri-procedural bleeding, associated with adverse outcomes after PCI, has declined notably in recent years.[52] Radial access has probably contributed (see above) but other bleeding avoidance strategies have been emphasised in a study of 1,522,935 patients entered in the National Cardiovascular Data Registry CathPCI Registry.[53] The study showed that vascular closure devices and bivalirudin therapy together were associated with a reduction of bleeding events from 2.8% to 0.9%, yet these strategies were used least often in patients with a high pre-procedural risk of bleeding assessed with the National Cardiovascular Data Registry bleeding risk model.[54] Based on these findings it seems clear that there remains considerable scope for improving the safety of PCI by pre-procedural identification of patients with most to gain from individualised bleeding avoidance strategies.

Myocardial injury

Myocardial injury during PCI is common and a recent meta-analysis of 15 studies embracing 7,578 patients found troponin elevation in 28.7% of procedures.[55] Any level of raised troponin was associated with an increased risk of cardiovascular events and for those with MI according to the universal definition[56] the OR for major adverse cardiac events at 18 months was 2.25 (1.26 to 4.00). Direct evidence of peri-procedural myocardial injury has now been made available from cardiovascular magnetic resonance imaging, which documented new myocardial hyperenhancement (median mass 5.0 g) in 32% of 152 patients undergoing PCI. After adjustment for age and sex, these patients had a 3.1-fold (95% CI 1.4 to 6.8; p=0.004) higher risk of adverse outcome than patients without new hyperenhancement.[57] These data have enhanced interest in

ku PCI. Nakon usklađivanja za dob i spol, ovi pacijenti su imali 3,1 puta (95% CI 1,4 do 6,8; p=0,004) viši rizik od nepovoljnih ishoda od pacijenata bez hiperpovećanja.[57] Ovi podaci su povećali interes za farmakološke i mehaničke intervencije usmjerene ka zaštiti miokarda tijekom elektivne PCI. Visoke doze statina su u tom pogledu obećavajuće, a u jednoj studiji sa 668 pacijenata koji ranije nisu uzimali statine, periproceduralni infarkt miokarda (definiran kao elevacija CK-MB >3x gornje granice normale) je nastupio kod 9,5% od onih randomiziranih na jednu udarnu dozu od 80 mg atorvastatina, u usporedbi s 15,8% u kontrolnoj skupini.[58] Većina pacijenata bi već trebala uzimati statine i prije elektivne PCI, no za one koji ih ne uzimaju, ovi podaci ukazuju da je prijeproceduralno doziranje zajedno s acetilsalicilnom kiselinom i klopidogrelom značajno sredstvo povećanja sigurnosti pacijenata. Također je obećavajuće i ishemijsko predkondicioniranje, koje je u nedavnoj studiji s 242 pacijenta podvrgnutih elektivnom PCI bilo povezano sa smanjenim otpuštanjem troponina I nakon 24 sata u usporedbi s kontrolnom skupinom (0,06 naspram 0,16 ng/ml; p=0,040).[59] Učestalost glavnih nepovoljnih kardioloških i cerebralnih epizoda nakon 6 mjeseci također je bila niža u skupini s ishemijskim predkondicioniranjem (4 naspram 13 epizoda; p=0,018). Međutim, ovo je bila mala otvorena studija te je potrebno daljnje istraživanje prije no što će se ovaj jeftin način zaštite miokarda moći preporučiti u rutinskoj kliničkoj praksi.

PCI kod posebnih skupina

Prethodna radioterapija

Torakalna radioterapija kod žena s karcinomom dojke je povećala dugoročni rizik od kardiovaskularne smrti,[60] moguće induciranjem kontinuiranog upalnog odgovora u ozračenim arterijama.[61] Također je povezana s nepovoljnim ishodima za koronarni stenting, uz omjer šansi za smrt od svih uzroka nakon 6 godina od 4,2 (95% CI 1,8 do 9,5) u usporedbi s pacijentima koje nisu podvrgnute radioterapiji.[62]

Dijabetes

CABG je već dugo preferirana strategija revaskularizacije kod pacijenata s dijabetesom i višežilnom KBS, a objava studija BARI-2D i CARDia je učinila vrlo malo kako bi se osporilo ovo ortodoksno mišljenje. U BARI-2D istraživanju, 2.368 pacijenata s dijabetesom tipa 2 (31% s trožilnom bolesti) je stratificirano na prikladne za ili PCI ili CABG i zatim randomizirano na suvremenu farmakološku terapiju ili revaskularizaciju.[63] Nakon praćenja u prosječnom trajanju od 5,3 godine, učestalosti smrtnog ishoda od svih uzorka (primarni ishod) su bile slične i za skupinu s farmakološkim liječenjem i revaskularizacijom, no kod CABG skupine, pacijenti koji su bili dodijeljeni na revaskularizaciju su imali nižu učestalost kardiovaskularnih događaja (smrt, infarkt miokarda ili moždani udar) od pacijenata liječenjih farmakološki. Također, pacijenti u studiji BARI-2D koji su randomizirani na revaskularizaciju su imali veću dobrobit na simptome od skupine liječene farmakološki.[64]

U studiji CARDia, 510 pacijenata s dijabetesom, od kojih je 93% imalo višežilnu bolest, bilo je randomizirano na PCI ili CABG.[65] Zajednički ishod od smrtnosti od svih uzroka, nefatalnog infarkta mioakrda i nefatalnog moždpharmacological and mechanical interventions directed at protecting the myocardium during elective PCI. High-dose statins show promise in this regard, and in one study of 668 statin-naive patients, peri-procedural MI (defined as a CK-MB elevation >3x upper limit of normal) occurred in 9.5% of those randomised to a single loading dose of atorvastatin 80 mg, compared with 15.8% in the control group.[58] Most patients should already be taking statins before elective PCI but for those who are not, these data indicate that pre-procedural loading together with aspirin and clopidogrel is a potential means of enhancing patient safety. Also promising is remote ischaemic preconditioning, which in a recent randomised trial of 242 patients undergoing elective PCI was associated with reduced troponin I release at 24 h compared with controls (0.06 vs 0.16 ng/ml; p=0.040).[59] The major adverse cardiac and cerebral event rate at 6 months was also lower in the remote ischaemic preconditioning group (4 vs 13 events; p=0.018). However, this was a small unblinded trial and further research is needed before this inexpensive means of myocardial protection can be recommended in routine clinical practice.

PCI in special groups

Prior radiotherapy

Thoracic radiotherapy in women with breast cancer increases the long-term risk of cardiovascular death,[60] possibly by induction of a sustained inflammatory response in irradiated arteries.[61] It is also associated with adverse outcomes for coronary stenting, with a HR for all-cause death after 6 years of 4.2 (95% CI 1.8 to 9.5) compared with people who have not undergone radiotherapy.[62]

Diabetes

CABG has long been the preferred revascularisation strategy in patients with diabetes and multivessel disease, and the publication of BARI-2D and CARDia has done little to challenge this orthodoxy. In BARI-2D, 2,368 patients with type 2 diabetes (31% with three-vessel disease) were stratified as being appropriate for either PCI or CABG and then randomised to contemporary medical treatment or revascularisation.[63] After follow-up for an average of 5.3 years, rates of all-cause mortality (the primary end point) were similar for the medical and revascularisation groups, but in the CABG stratum, patients assigned to revascularisation had lower cardiovascular event rates (death, MI or stroke) than patients assigned to medical treatment. However, the patients in BARI-2D randomised to revascularisation obtained greater symptomatic benefit than the medically treated group.[64]

In CARDia, 510 patients with diabetes, 93% of whom had multivessel disease, were randomised to PCI or CABG.[65] The composite rate of all-cause mortality, non-fatal MI, and non-fatal stroke at 1 year was 13.0% for PCI and 10.5% for CABG; this difference was not statistically significant but the study was powered and non-inferiority for PCI compared with CABG was not confirmed. It is the BARI-2D findings, therefore, that generated greater interest by showing that contemporary medical treatment of diabetic patients with complex CAD compares favourably with revascularisation.

danog udara je nakon 1 godine iznosila 13,0% za PCI i 10,5% za CABG; ova razlika nije bila statistički značajna, a neinferiornost PCI u usporedbi s CABG nije potvrđena. Stoga su rezultati studije BARI-2D stvorili veliki interes pokazujući da se suvremena farmakološka terapija dijabetičara s kompleksnom KBS može povoljno uspoređivati s revaskularizacijom.

Ishodi PCI

Ishodi PCI (i CABG) se i dalje kontinurano poboljšavaju.[66] Čimbenici rizika koji prije intervencije ukazuju na nepovoljan ishod su dobro definirani i uključuju oslabljenu funkciju lijeve klijetke, morfološki složene lezije, hitne postupke i dijabetes. Na ovaj popis se može dodati ljestvica EuroSCORE, koja je pokazala izvrsnu diskriminaciju za predviđanje bolničke smrtnosti (područje pod ROC krivuljom 0,91 (95% CI 0,86 do 0,97)) na 1.173 pacijenta liječenih PCI, uz šanse za smrtni ishod koje su se povećavale s porastom vrijednosti ljestvice.[67] EuroSCORE je već potvrđen i koristi se naširoko kod predviđanja kirurških rizika, a autori predlažu da je stoga u dobroj poziciji da pomogne kardiolozima i kardiokirurzima da individualiziraju profil rizika svakog pacijenta, kako bi bolje odabrali odgovarajuću strategiju revaskularizacije. Potrebna je vanjska potvrda EuroSCORE u drugim skupinama pacijenata liječenih PCI prije no što se njegova klinička primjena može sa sigurnošću preporučiti. U međuvremenu SYNTAX ljestvica, temeljena na specifičnim anatomskim značajkama koronarnog angiograma, ostaje najbolji potvrđeni način predviđanja rizika PCI i CABG, iako je njezina vrijednost kod predviđanja 12-mjesečnih ishoda ograničena na PCI.[68]

Druga generacija stentova koji otpuštaju lijekove

Uporaba DES je rezultirala značajnim sniženjem nastanka restenoze u usporedbi s metalnim stentovima (BMS), iako uz povećan rizik kasne tromboze stenta.[69] Ovo je dalo poticaj za dizajniranje učinkovitije, druge, generacije DES koja predstavlja i temu istraživanja u četiri najnovije studije, koje su sve dizajnirane za kliničke događaje s primarnim zajedničkim ishodom koji se sastoji od srčane smrti, infarkta miokarda ili revaskularizacije ciljne žile. Najveća od njih, studija SPIRIT IV, randomizirala je 3.687 pacijenata u omjeru 2:1 na liječenje drugom generacijom stentova koji otpuštaju everolimus (EES) ili prvom generacijom stentova koji otpuštaju paklitaksel (PES).[70] Studija je potvrdila nadmoć EES nad PES za zajednički ciljni ishod (4,2% nasuprot 6,8%) te također za trombozu stenta (0,2% nasuprot 0,8%). COMPARE studija provedena u jednom centru je usporedila drugu generaciju EES s drugom generacijom PES na 1800 pacijenata i ponovo utvrdila prednost EES, koja je nakon 12 mjeseci bila povezana s 6% učestalosti primarnih ishoda u usporedbi s 9% u PES skupini.[71] Druga generacija stentova koji otpuštaju zotarolimus (ZES) je uspoređena sa stentovima koji luče sirolimus (SORT OUT III, n=2332) i EES (Resolute All Comers studija, n=2292). U studiji SORT OUT III, ZES se pokazao inferiornim u usporedbi sa SES, uz stope primarnog ishoda od 6% nasuprot 3%, a razlika je održana i do 18 mjeseci.[72] U studiji Resolute All Comers zajednički klinički ishodi nakon 1 godine su bili gotovo identičnih (8,2% i 8,3%) udjela u ZES i EES skupinama, no ZES skupina je pokazala tendenciju

Outcomes for PCI

Outcomes for PCI (and for CABG) continue to improve.[66] Pre-procedural risk factors for adverse outcomes are well defined and include impaired LV function, complex lesion morphology, emergency procedures and diabetes. To this list may now be added the EuroSCORE, which showed excellent discrimination for predicting hospital mortality (area under the receiver operating characteristic curve 0.91 (95% CI 0.86 to 0.97)) in 1,173 PCI patients, with the odds of death increasing as the score rose.[67] The EuroSCORE is already validated and widely used to predict surgical risk and the authors suggest that it is therefore well placed to help cardiologists and cardiac surgeons individualise the risk profile of patients in order to better select the appropriate revascularisation strategy. External validation of the EuroSCORE in other PCI cohorts is now needed before its clinical application can be confidently recommended. Meanwhile the SYNTAX score, based on specific anatomical characteristics of the coronary angiogram, remains the best validated means of anticipating the risks of PCI and CABG, although its value for predicting 12-month outcomes is confined to PCI.[68]

Second-generation DES

DES have produced important reductions in rates of restenosis compared with bare metal stents (BMS), albeit at increased risk of late stent thrombosis.[69] This has provided impetus for the design of more effective 'second-generation' DES that have been the subject of investigation in four recent trials, all of which were powered for clinical events with a primary composite end point of cardiac death, MI, or target-vessel revascularisation. The largest of these, SPIRIT IV, randomised 3,687 patients in a 2:1 ratio to receive second-generation everolimus-eluting stents (EES) or first-generation paclitaxel-eluting stents (PES).[70] The study confirmed superiority of EES over PES for the composite clinical end point (4.2% vs 6.8%), and also for stent thrombosis (0.2% vs 0.8%). The single-centre COMPARE trial compared second-generation EES with second-generation PES in 1,800 patients and again showed superiority of the EES, which at 12 months was associated with a 6% incidence of the primary end point compared with 9% in the PES group.[71] The second-generation zotarolimus-eluting stent (ZES) has been evaluated against sirolimus-eluting (SORT OUT III, n=2,332) and EES (Resolute All Comers Trial, n=2,292). In SORT OUT III, ZES proved inferior to SES, with primary end point rates of 6% versus 3%, a difference sustained at 18 months.[72] In Resolute All Comers the composite clinical end point at 1 year occurred in almost identical (8.2% and 8.3%) proportions of ZES and EES groups, but the ZES group showed a tendency for more frequent stent thrombosis (2.3% vs 1.5%) and greater in-stent late lumen loss (0.27 mm vs 0.19 mm). These observations raise further concerns about ZES that will not be resolved until the 5-year follow-up data become available.[73] Long-term results of ZES have been favourable in registries,[74] but the results of these four randomised trials have ensured that second-generation EES are now the first choice for most interventionists.

češće tromboze stenta (2,3% nasuprot 1,5%) i viši kasni gubitak lumena u stentu (0,27 mm nasuprot 0,19 mm). Ova opažanja pobuđuju daljnju zabrinutost o ZES koja se neće razriješiti sve dok podaci petogodišnjeg praćenja ne postanu dostupni.[73] Dugoročni rezultati ZES su u registrima bili povoljni,[74] no rezultati ove četiri randomizirane studije su utvrdili da je druga generacija EES sada prvi izbor većine intervencijskih kardiologa.

Ako se pomaknemo dalje od druge generacije DES, u kliničku arenu sada ulazi DES bez polimera i DES s biorazgradivim polimerom. Randomizirana usporedba otpuštanja rapamicina pomoću ovih novih platformi nasuprot konvencionalnim (trajnim) polimerima presvučenim stentovima koji luče sirolimus, pokazala je usporedivu sigurnost i učinkovitost za prevenciju kliničke restenoze tijekom dvogodišnjeg praćenja. Međutim, angiografsko praćenje je potvrdilo održiviju neointimalnu supresiju uz stent bez polimera koji luči rapamicin nego s ostalim platformama.[75] Otpuštanje everolimusa pomoću biorazgradivog stenta je kod 30 pacijenata također dalo impresivne dvogodišnje ishode bez srčanih smrti, ishemijom potaknutih revaskularizacija ciljnih lezija ili registrirane tromboze stenta.[76] Zanimljivo je da je nakon biorazgrađivanja u stentiranom segmentu nastupio povrat vazomocije. Ovi rezultati će bez sumnje osigurati kontinuirani interes za razvoj DES bez polimera.

Metalni stentovi

Prednosti koje pruža DES pri zbrinjavanju KBS rezultiraju kontiniranim smanjenjem, pa sve do nestanka, indikacija za implantaciju BMS. Nadmoć DES u usporedbi s BMS za primarnu PCI utvrđena je značajno nižim stopama revaskularizacije ciljne lezije, a najnoviji podaci pokazuju da dobrobit postoji i nakon 3 godine (9,4% nasuprot 15,1%) bez značajnih razlika u učestalosti smrtnog ishoda, ponovnog infarkta ili tromboze stena.[77] Trenutne preporuke daju prednost primjeni DES kod infarkta miokarda s ST-elevacijom, naročito kod pacijenata s visokorizičnim značajkama za restenozu kao što su duge lezije, male žile ili dijabetes.[78] Studija BASKET-PROVE sada također osporava stav da BMS imaju rezidualne indikacije u velikim koronarnim arterijama.[79] Randomizirano je bilo 2.314 pacijenata koji su trebali koronarne stentove promjera od 3-4 mm na SES prve generacije, EES druge generacije ili kobalt-krom BMS. Nakon dvije godine udjeli kardiovaskularnih epizoda i udjeli tromboze stentova su bili usporedivi u sve tri skupine, no udjeli klinički vođenih revaskularizacija su bili svega 4,3% sa SES i 3,7% sa EES u usporedbi s 10,3% s BMS. Iako nije bilo izvješća o troškovnoj učinkovitosti, ovi nalazi potvrđuju da se dobrobit DES za sigurnost i zaštitu od restenoze malih koronarnih arterija može proširiti i na postupke na većim žilama.

Balon presvučen paklitakselom

Postupak PCI u vrlo malim žilama (<3 mm) i dalje ostaje izazov. Upotreba DES je poboljšala sigurnost i dugoročne ishode u odnosu na BMS,[80] a u randomiziranim studijama se za restenozu nakon 6 mjeseci pokazao bolji od novog balona presvučenog paklitakselom.[81] No ipak, sada je identificirana potencijalno važna koronarna primjena balona presvučenog paklitakselom za liječenje restenoze u stentu. Nedavna randomizirana studija sa 131 pacijenata s

Moving beyond the second generation of DES, polymer-free and biodegradable polymer DES are now entering the clinical arena. A randomised comparison of rapamycin delivery using these novel platforms versus conventional (permanent) polymer coated sirolimus-eluting stents, showed comparable safety and comparable efficacy for prevention of clinical restenosis during the 2-year follow-up. However, angiographic surveillance confirmed more sustained neointimal suppression with the polymer-free rapamycin-eluting stent than with the other platforms.[75] Everolimus delivery by a bioabsorbable stent in 30 patients also produced impressive 2-year outcomes with no cardiac deaths, ischaemia-driven target lesion revascularisations, or stent thromboses recorded.[76] Interestingly, vasomotion was restored in the stented segment after bioabsorption. These results will doubtless ensure continuing interest in the development of polymer-free DES.

Bare metal stents

The advantages offered by DES in management of CAD have seen continuing indications for BMS diminish almost to the point of extinction. The superiority of DES compared with BMS for primary PCI is driven by significantly lower rates of target lesion revascularisation, and recent data show that the benefit is sustained after 3 years (9.4% vs 15.1%) with no significant differences in the rates of death, reinfarction, or stent thrombosis.[77] Current recommendations are for the preferential use of DES in ST elevation myocardial infarction, particularly in patients with high-risk features for restenosis such as long lesions, small vessels, or diabetes.[78] The BASKET-PROVE study now also challenges the notion that BMS have residual indications in large coronary arteries.[79] These investigators randomised 2,314 patients requiring 3-4mm diameter coronary stents to receive first-generation SES, second-generation EES, or cobalt-chromium BMS. After 2 years cardiovascular event rates and rates of stent thrombosis were comparable between the three groups, but the rates of clinically driven target lesion revascularisation were only 4.3% with SES and 3.7% with EES compared with 10.3% with BMS. Although cost-effectiveness was not reported, these findings confirm that the benefits of DES for safety and protection against restenosis in small coronary arteries extend to procedures undertaken in larger vessels.

Paclitaxel-coated balloon

PCI in very small vessels (<3 mm) remains a challenge. Use of DES has improved safety and longer-term outcomes relative to BMS,[80] and in a randomised trial proved better than the newly available paclitaxel-coated balloon for restenosis after 6 months.[81] Nevertheless, a potentially important coronary application of the paclitaxel-coated balloon for treatment of in-stent restenosis has now been identified. A recent randomised trial in 131 patients with bare metal in-stent restenosis reported 6-month binary restenosis rates of only 7% for the drug-coated balloon compared with 20% for a paclitaxel-eluting stent.[82] However, longer-term data will be needed. A recent registry study reported that SES used for treatment of bare metal in-stent restenosis exhibited sustained efficacy at 4 years with a target lesion revascularisation rate of only 11.1%.[83]

restenozom u metalnom stentu je izvijestila o stopama binarne restenoze nakon 6 mjeseci od samo 7% za balon presvučen lijekom u usporedbi s 20% za stent koji luči paklitaksel.[82] Međutim, nužno su potrebni dugoročni podaci. Nedavna studija s podacima iz registara je izvijestila da SES korišten za liječenje restenoze u metalnom stentu pokazuje kontinuiranu učinkovitost nakon 4 godine uz učestalost revaskularizacije ciljane lezije od 11,1%.[83]

Antitrombocitna terapija

Tromboza stenta

Dvostruka antitrombocitna terapija s acetilsalicilnom kiselinom (ASK) i klopidogrelom (DAPT) se smatra osnovnim dodatkom kod PCI u svrhu zaštite od tromboze stenta. Smjernice preporučuju da se DAPT nastavi u trajanju od 12 mjeseci kod pacijenata koji su primili DES kako bi se dopustila potpuna endotelizacija žičice stenta, nakon čega se liječenje može nastaviti isključivo ASK. Međutim, vrlo kasna tromboza stenta ostaje ozbiljan razlog za zabrinutost te je dobila pažnju mnogih novijih studija bilo evaluacijom potencijalnih dobrobiti produljenja DAPT na više od 12 mjeseci ili titriranjem antitrombocitne terapije u odnosu na rezultate testova funkcije trombocita. Učinak produljenog DAPT na više od 12 mjeseci je procijenjen u studiji s podacima iz registra, koja je ustanovila da nema dodatne zaštite od smrti ili infarkta miokarda u usporedbi s DAPT ≤12 mjeseci.[84] Ovo je potvrđeno u randomiziranoj studiji kontinuirane terapije ASK i klopidogrelom nasuprot terapiji ASK u 2.701 pacijenata koji su već primali DAPT 12 mjeseci nakon PCI.[85] Nakon 2 godine praćenja, učestalost infarkta miokarda i smrti su bile slične u obje skupine (1,8% naspram 1,2%), što je dalo podršku za preporuku da se DAPT nastavi u trajanju od 12 mjeseci nakon PCI s implantacijom DES. Međutim, važnost strogog pridržavanja DAPT u prvih 12 mjeseci je naglašena nalazima još jedne nedavne studije koja je ustanovila da su pacijenti koji su odgodili uzimanje klopidogrela nakon otpusta iz bolnice imali gotovo dvostruko viši rizik od infarkta miokarda ili smrti u usporedbi s onima koji su počeli lijek uzimati na dan otpusta iz bolnice, iako je to kašnjenje iznosilo svega 3 dana.[86]

Visoka rezidualna trombocitna reaktivnost

Alternativni pristup za zaštitu od tromboze stenta čini agresivniji pristup liječenju kod pacijenata s višom rezidualnom reaktivnosti trombocita nakon uzimanja klopidogrela. Čini se da su takvi pacijenti pod značajnim rizikom od neželjenih događaja, a u nedavnoj studiji sa 215 pacijenata podvrgnutih nezaštićenom PCI debla glavne lijeve koronarne arterije, rizik od srčane smrti unutar prve godine je bio više nego dvostruk kod onih s visokom rezidualnom trombocitnom aktivnost.[87] Istraživači studije GRAVITAS su sada izvijestili o svojoj randomiziranoj usporedbi standardne doze (75 mg) nasuprot visoke doze (150 mg) klopidogrela nakon stenta koji otpušta lijek s 2.214 pacijenata s visokom trombocitnom reaktivnosti.[88] Iako je visoka doza klopidogrela bila učinkovita u smanjenju trombocitne reaktivnosti, učestalost kardiovaskularnih događaja (smrt, infakt miokarda, tromboza stenta) nakon 6 mjeseci su bile identične do 2,3% u obje skupine. Neuspjeh agresivne antitrombocitne terapije da smanji učestalost epizoda kod pacijenata s visokom rezidualnom trombocitnom reaktivnosti je bio možda iznenađujući, no neće značiti završetak

Antiplatelet therapy

Stent thrombosis

Dual antiplatelet therapy with aspirin and clopidogrel (DAPT) is considered an essential adjunct to PCI to protect against stent thrombosis. Guidelines recommend that DAPT is continued for 12 months in patients who have received a DES to allow for complete endothelialisation of the struts, whereupon treatment can continue with aspirin alone. However, very late stent thrombosis remains a real concern and has received attention in a number of recent studies either by evaluating the potential benefits of prolonging DAPT beyond 12 months or by up-titrating antiplatelet therapy against the results of platelet function tests. The impact of prolonged DAPT beyond 12 months has been evaluated in a registry study, which found no additional protection against death or MI compared with DAPT for ≤12 months.[84] This was confirmed in a randomised trial of continuing aspirin and clopidogrel versus monotherapy with aspirin in 2,701 patients who had already received DAPT for 12 months after PCI.[85] At 2-years' follow-up, rates of MI and death were similar in the two groups (1.8% vs 1.2%), providing support for the guideline recommendation to continue DAPT for 12 months after PCI with DES. However, the importance of strict adherence to DAPT in the first 12 months is emphasised by the finding in another recent study that patients who delayed filling their prescription for clopidogrel after hospital discharge had almost twice the risk of MI or death compared with those who filled their prescription on the day of discharge, even though the median delay was only 3 days.[86]

High residual platelet reactivity

An alternative approach for protecting against stent thrombosis is to target more aggressive treatment at patients with high residual platelet reactivity after clopidogrel loading. Such patients appear to be at significantly increased risk of adverse events, and in a recent study of 215 patients undergoing unprotected left main stem PCI the risk of cardiac death at 1 year was more than doubled in those with high residual platelet activity.[87] The GRAVITAS investigators have now reported their randomised comparison of standard dose (75 mg) versus high-dose (150 mg) clopidogrel after drug-eluting stenting in 2,214 patients with high on-treatment platelet reactivity.[88] Although high-dose clopidogrel was effective in reducing platelet reactivity, cardiovascular event rates (death, MI, stent thrombosis) after 6 months were identical at 2.3% in both groups. The failure of aggressive antiplatelet treatment to reduce event rates in patients with high residual platelet reactivity was, perhaps, surprising but will not be the last word on this subject, as other such studies are in progress. Meanwhile, calls for platelet reactivity monitoring in patients receiving clopidogrel seem premature.[89]

A potential mechanism of high residual platelet reactivity in some patients treated with clopidogrel relates to conversion of the prodrug to an active metabolite by the hepatic cytochrome P-450 system. Conversion is genetically determined and is reduced in carriers of common loss-of-function CYP alleles, who show decreased platelet inhibition and a 1.53 to 3.69 increased risk of cardiovascular events compared with non-carriers.[90-92] This led to calls

rasprave na ovu temu, pošto su druge slične studije u tijeku. U međuvremenu, zahtjevi za nadzor trombocitne reaktivnosti kod pacijenata koji primaju klopidogrel se čine preuranjenima.[89]

Potencijalni mehanizam visoke rezidualne trombocitne reaktivnosti kod nekih pacijenata liječenih klopidogrelom se odnosi na konverziju prolijeka u aktivni metabolit posredstvom jetrenog citokrom P-450 sustava. Konverzija je genetski određena te je smanjena kod nosioca uobičajenog gubitka funkcije CYP alela, koji pokazuju smanjenu trombocitnu inhibiciju i od 1,53 do 3,69 povećani rizik od kardiovaskularnih događaja u usporedbi s ne-nosiocima.[90-92] Ovo je dovelo do poziva za višim doziranjem klopidogrela kod nosioca gubitka funkcije alela, no ova politika je sada dovedena u pitanje od strane studije koja je stratificirala pacijente uključene u dvije velike randomizirane studije terapije klopidogrelom prema genotipnom statusu.[93] Niti u jednoj studiji status nosioca gubitka funkcije nije utjecao na primarne zajedničke ishode, ili ishode sigurnosti u odnosu na krvarenje. Autori su zaključili da bi nosioci gubitka funkcije CYP alela trebali primati klopidogrel prema trenutno preporučenim dozama za akutni koronarni sindrom, iako je za atrijsku fibrilaciju zaključak kvalificiran potrebom za većim studijama. U međuvremenu, genotipiranje pacijenata s akutnim koronarnim sindromom u usporedbi klopidogrela s tikagrelorom (PLATO) je izvijestilo da je rizik od primarnih ishoda bio niži kod pacijenata randomiziranih na ticagrelor u usporedbi s klopidogrelom no relativna redukcija rizika nije bila pod utjecajem CYP ili ABCB1 (kodiranje za apsorpciju klopidogrela u svrhu utjecaja na proteine) genotipa.[94] Stoga, prema trenutnim dokazima, ne čini se da genetsko testiranje pomaže kod određivanja učinkovitosti klopidogrela u usporedbi s placebom ili tikagrelorom te je malo vjerojatno da će pružiti korisan temelj za određivanje strategije doziranja.

Interakcija lijekova

Još jedan potencijalan mehanizam visoke rezidualne trombocitne reaktivnosti kod nekih pacijenata koji primaju inhibitore trombocita jest interakcija s nekim inhibitorima protonske pumpe (PPI), koji mogu umanjiti konverziju klopidogrela na njegove aktivne metabolite ometajući citokrom P-450 sustav te također može umanjiti trombocitni odgovor na ASK.[95] Međutim, u studiji s velikim skupinama ispitanika, učestalost epizoda među pacijentima otpuštenima s PPI se povećala neovisno o tome jesu li također bili otpušteni na klopidogrelu, što ukazuje da interakcija nije bila odgovorni mehanizam.[96] Štoviše, studija COGENT sa 3.873 pacijenta koji su primili DAPT i bili randomizirani na omeprazol ili placebo je bila ohrabrujuća jer nije pokazala razliku u primarnim kardiovaskularnim ishodima, složenom od smrti od kardiovaskularnih uzroka, ne-fatalnog infarkta miokarda, revaskularizacije ili moždanog udara.[97] Studija CONGENT je ustanovila da su pacijenti randomizirani na omeprazol imali značajno nižu učestalost gastrointestinalnog krvarenja te uzimajući u obzir gastroprotektivne učinke PPI kod pacijenata na niskim dozama ASK, nedavno potvrđeno studijom OBERON,[98] čini se da su koristi veće od potencijalnog rizika povezanog s interakcijom s klopidogrelom. Ostali lijekovi koji su nedavno došli na razmatranje uključuju blokatore kalcijskih kanala koji se, kao i PPI-i, metaboliziraju pomoću hepatičkog citokromnog P-450 sustava i stoga imaju potencijal za interakciju s klopidogrelom. Opservacijski podaci na pacijentima koji

for higher clopidogrel dosing in carriers of the loss-of-function alleles but this policy has now been questioned by a study that stratified patients enrolled in two large randomised trials of clopidogrel therapy by genotype status.[93] In neither trial did loss-of-function carrier status affect the primary composite efficacy outcomes, or safety outcomes with respect to bleeding. The authors concluded that carriers of loss-of-function CYP alleles should receive clopidogrel at currently recommended doses in ACS, although for atrial fibrillation the conclusion was qualified by a need for larger studies. Meanwhile, genotyping of patients with ACS enrolled in a head-to-head comparison of clopidogrel with ticagrelor (PLATO) reported that the hazard of the primary endpoint was lower for patients randomised to ticagrelor compared with clopidogrel but RR reduction was unaffected by CYP or ABCB1 (coding for a protein influencing clopidogrel absorption) genotype.[94] On present evidence, therefore, genetic testing does not appear to be helpful in determining clopidogrel's effectiveness in comparison with placebo or ticagrelor and is unlikely to provide a useful basis for determining dosing strategies.

Drug interaction

Another potential mechanism of high residual platelet reactivity in some patients receiving platelet inhibitors is an interaction with some proton pump inhibitors (PPIs), which may reduce clopidogrel's conversion to its active metabolite by interfering with the hepatic cytochrome P-450 system and may also reduce the platelet response to aspirin.[95] However, in a large cohort study event rates among patients discharged on PPIs were increased independently of whether or not they were also discharged on clopidogrel, indicating that drug interaction was not the responsible mechanism.[96] Moreover, the COGENT trial of 3,873 patients receiving DAPT and randomised to omeprazole or placebo was reassuring in showing no difference in the primary cardiovascular end point, a composite of death from cardiovascular causes, non-fatal myocardial infarction, revascularisation, or stroke.[97] COGENT found that patients randomised to omeprazole had a significantly lower rate of gastrointestinal bleeding and, given the gastro-protective effects of PPIs in patients on low-dose aspirin, recently confirmed in the OBERON trial,[98] the benefits seem to outweigh any potential risk related to clopidogrel interaction. Other drugs that have come under recent scrutiny include calcium channel blockers which, like PPIs, are metabolised by the hepatic cytochrome P-450 system and have the potential therefore to interact with clopidogrel. Observational data in patients taking clopidogrel have shown that high residual platelet reactivity is more common in those co-prescribed calcium channel blockers than in those who are not,[99] and an earlier observational study reported that this may be associated with a higher cardiovascular event rate 2 years after PCI.[100] Interpretation of these studies needs to be cautious, however, and more prospective data are needed, ideally in the form of randomised trials.

Coronary artery bypass surgery in stable coronary disease

Among key technical innovations of the last 15 years has been off-pump CABG but its potential benefits for my-

su uzimali klopidogrel su pokazali da je visoka rezidualna trombocitna reaktivnost uobičajenija kod onih kojima su usporedno propisani blokatori kalcijskih kanala nego kod onih kod kojih nisu[99], a ranija studija je izvijestila da je ovo možda povezano s učestalosti kardiovaskularnih epizoda dvije godine nakon PCI.[100] Međutim, interpretacija ovih studija mora biti kontinuirana i potrebno je više prospektivnih podataka, idealno u obliku randomiziranih studija.

Ugradnja aortokoronarnih premosnica kod stabilne koronarne bolesti srca

Među ključnim tehničkim inovacijama u posljednjih 15 godina je i CABG bez izvantjelesnog krvotoka (*off-pump*) no njegove potencijalne koristi za zaštitu miokarda i cerebruma je trebalo procijeniti s obzirom na probleme nepotpune revaskularizacije i izvješća o povećanom riziku od infarkta miokarda i rano trošenje premosnice u usporedbi s postupcima u kojima se koristi izvantjelesni krvotok (on-pump). Dvije randomizirane studije su sada razjasnile neka od ovih pitanja. Istraživači u studiji ROOBY su randomizirali 2.203 pacijenta na "on-pump" ili "off-pump" CABG i nisu našli značajne razlike u učestalosti 30-dnevnih zajedničkih ishoda (7,0% naspram 5,6% za smrt, ponovnu operaciju, novu mehaničku potporu, srčani zastoj, komu, moždani udar ili zatajenje bubrega).[101] Nakon 1 godine isti zajednički ishod je bio viši za off-pump nego za on-pump CABG (9,9% naspram 7,4%, p=0,04) i prohodnost premosnice je bila niža (82,6% naspram 87,8%, p<0,01) kod 1.371 pacijenta koji su imali popratnu angiografiju. U međuvremenu, pažljiva procjena 12-mjesečnih kognitivnih ishoda nije pronašla razliku između skupina, iako je učestalost oštećenja u oba postupka bila uvjerljivo niska.[102]

Kratko nakon izvješća ROOBY, 'Best Bypass Surgery' ispitivači su objavili svoje rezultate za visokorizičnu skupinu (EuroSCORE≥5, trožilna bolest) od 341 pacijenta randomiziranih na on-pump ili off-pump CABG.[103] Ponovo, zajednički primarni ishod (smrtnost od svih uzroka, akutni infarkt miokarda, srčani zastoj s uspješnim oživljavanjem, sindrom niskog volumena srca/kardiogeni šok, moždani udar i koronarna reintervencija) je bio sličan za on-pump i off-pump skupine (15% i 17%; p=0,48) i nakon 3 godine smrtnost od svih uzroka je značajno porasla u off-pump skupini (24% naspram 15%, HR 1,66, 95% CI 1,02 do 2,73; p=0,04).[104] Ove studije nisu dale dokaze o kliničkoj nadmoći off-pump CABG, iako je prerano razmatrati o napuštanju ovog postupka. Konvencionalna kardiopulmonarna premosnica ima važne štetne učinke koji uključuju aktivaciju trombocita i neutrofila, potrošnju koagulacijskih faktora, generiranje komplementa i ispuštanje proinflatornih mediatora uz generiranje sistemskog upalnog odgovora. Ako off-pump operativni zahvati ne mogu pružiti bolje kliničke ishode možda bi bilo mudro poslušati urednike i razmotriti "bolje premosnice" u obliku minijaturiziranih sustava premosnica.[105] Ovo je bila tema nedavne meta-analize koja je ustanovila da je minijaturizina kardiopulmonarna premosnica u usporedbi s konvencionalnom kardiopulmonarnom premosnicom u neposrednom postoperativnom razdoblju povezana s ponešto nižom stopom smrtnosti (1,1% naspram 2,2%, OR 0,58%, 95% CI 0,23 do 1,47, p=0,25) i moždanih udara (0,2% naspram 2,0%, OR 0,25, 95% CI 0,06 do 1,00, p=0,05).106 Sada su potrebne veće studije kako bi se dalje procijenile minijaturizirane kardiopulmonarne premosnice.

ocardial and cerebral protection have had to be weighed against problems of incomplete revascularisation and reports of an increased risk of MI and early graft attrition compared with on-pump procedures. Two randomised trials have now clarified some of these issues. The ROOBY investigators randomised 2,203 patients to on-pump or off-pump CABG and found no significant difference in rates of the 30-day composite outcome (7.0% vs 5.6%, respectively for death, reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure).[101] After 1 year the same composite was higher for off-pump than for on-pump CABG (9.9% vs 7.4%, p=0.04) and graft patency was lower (82.6% vs 87.8%, p<0.01) in the 1,371 patients who had follow-up angiography. Meanwhile, a careful assessment of 12-month cognitive outcomes found no difference between the groups, although the rate of impairment by either procedure was reassuringly low.[102]

Shortly after the ROOBY report, the 'Best Bypass Surgery' trialists published their results in a higher risk group (EuroSCORE ≥5, three-vessel disease) of 341 patients randomised to on-pump or off-pump CABG.[103] Again, the composite primary outcome (all-cause mortality, acute MI, cardiac arrest with successful resuscitation, low cardiac output syndrome/cardiogenic shock, stroke, and coronary reintervention) was similar for the on-pump and off-pump groups (15% and 17%; p=0.48) and after 3 years all-cause mortality was significantly increased in the off-pump group (24% vs 15%; HR 1.66, 95% CI 1.02 to 2.73; p=0.04).[104] These trials have not provided evidence of clinical superiority for off-pump CABG, although it is premature to consider abandoning the procedure. Conventional cardiopulmonary bypass has important deleterious effects that include platelet and neutrophil activation, consumption of coagulation factors, complement generation and the release of proinflammatory mediators with generation of a systemic inflammatory response. If off-pump surgery cannot deliver better clinical outcomes it may be prudent to take heed of the editorialist and consider 'better-bypass' in the form of a miniaturised bypass system[105] This was the subject of a recent meta-analysis which found that miniaturised cardiopulmonary bypass in comparison with conventional cardiopulmonary bypass was associated with a somewhat lower rate of death (1.1% vs 2.2%, OR 0.58, 95% CI 0.23 to 1.47, p=0.25) and stroke (0.2% vs 2.0%, OR 0.25, 95% CI 0.06 to 1.00, p=0.05) in the immediate postoperative period.[106] Now needed are larger trials to further evaluate miniaturised cardiopulmonary bypass.

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