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Almanac 2013.: stabilna koronarna bolest srca

Almanac 2013: stable coronary artery disease

Shahed Islam, Adam Timmis*

Barts and the London School of Medicine and Dentistry, London Chest Hospital, London, Ujedinjeno Kraljevstvo

Barts and the London School of Medicine and Dentistry, London Chest Hospital, London, United Kingdom

KORONARNA BOLEST SRCA SE SMANJUJE

Epidemiološki podaci iz Europe, SAD i drugdje u razvijenom svijetu pokazuju nagli pad smrtnosti od koronarne bolesti srca (KBS) tijekom posljednjih 40 godina.[1] Zabrinutost zbog izjednačavanja stope smrtnosti u mlađih odraslih[2] donekle je ublažena podacima iz Nizozemske koji pokazuju da su se kod muškaraca u dobi <55 godina stope smanjivanja ponovno ubrzale, povećanjem od samo 16% u razdoblju od 1993. do 1999. na 46% u razdoblju od 1999. do 2007.[3] Slično je uočeno kod mladih žena sa stopama smanjivanja 5% i 38% u istom vremenskom razdoblju. To je ohrabrujuće, osobito u kontekstu podataka iz Danske i Velike Britanije koji ukazuju na smanjivanje smrtnosti, kao i nagli pad standardizirane stope incidencije akutnog infarkta miokarda koji ukazuju da su koronarna prevencija, kao i liječenje akutnih faza bolesti pridonijele nedavnim trendovima pada mortaliteta.[4,5] U međuvremenu nas australska studija podsjeća da je infarkt miokarda jedna od nekoliko manifestacija kardiovaskularne bolesti, pri čemu ukazuje na to da su se smanjenja učestalosti i stope recidiva hospitaliziranih KBS od 2000. do 2007. godine također odnosile na cerebrovaskularne i bolesti perifernih arterija.[6]

Međutim, nisu sve epidemiološke vijesti dobre, a podaci iz Velike Britanije pokazuju da se poguban odnos između socioekonomskog statusa (SES) i KBS u posljednjih nekoliko godina ne umanjuje, gradijenti između gornjih i donjih skupina kvintila SES za bolničke prijeme su u načelu ostali nepromijenjeni u rasponu starosne dobi.[7] Da li to pridonosi gotovo trostrukom riziku od infarkta miokarda povezanog s mrtvorođenima i deveterostrukom riziku povezanog s ponovljenim spontanim pobačajima u novijoj njemačkoj studiji je nejasno, jer istraživači nisu pratili SES.[8] Isto tako nije jasno da li SES pridonosi trajnim etničkim razlikama u obje američke i britanske studije o smrtnosti od KBS iako se i drugi čimbenici smatraju bitnim. Dakle, afroamerički muškarci imaju veću izloženost čimbenicima rizika za KBS nego bijelci, a kada se podaci obrade nevezano, njihova sklonost za KBS nije veća, iako su stope smrtnosti dvostruko više.[9] Za afroameričke žene, učestalosti i stope smrtnosti su više nego kod žena bijelkinja. Ovi rezultati, koji ukazuju da izloženost čimbenicima rizika doprinosi etničkim razlikama u pojavnosti KBS, se u određenoj mjeri prikazuju i u nedavnom

CORONARY HEART DISEASE IN DECLINE

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

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

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izvješću Zdravstvenog istraživanja za Englesku u kojoj je 13.293 bijelaca i 2.120 azijata pristalo na praćenje smrtnosti.[10] Tjelesna neaktivnost je češće kod azijata u odnosu na bijelce (47% naspram 28%) čime smo objasnili >20% više njihove smrtnosti od KBS. U svakom slučaju novije mišljenje je da je povećana smrtnost među britanskim azijatima gotovo u cijelosti proizlazi iz njihove povećane osjetljivosti za bolest, a ne povećanim stopama smrtnosti oboljelih.[11]

DIJAGNOZA STABILNE KORONARNE BOLESTI SRCA

U najnovijim smjernicama AHA/ACC[12] naglašena je važnost individualiziranja dijagnostičkog protokola na temelju procijenjene vjerojatnosti KBS. U tom smislu, one preslikavaju ranije objavljene smjernice Nacionalnog instituta za kliničku izvrsnost (NICE) o pristupu dijagnosticiranja boli u prsima,[13] ali postoji značajna razlika u preporukama za neinvazivno testiranje. U novim smjernicom AHA/ACC daje se prednost ergometriji kao početnom dijagnostičkom postupku za većinu bolesnika, (NICE se ranije zalagao protiv korištenja ergometrije zbog relativno slabih dijagnostičkih dometa), a dijagnostika s famakološkim radionuklidima, srčanom magnetskom rezonancom (MRI) ili ehokardiografskim stres testom su opcije za bolesnike koji su nepodobni za test opterećenja. Preporuke za CT koronarografiju (CTCA) su oprezne, a klasična koronarografija se preopručuje u dijagnostičke svrhe samo ako su rezultati neinvazivnih testiranja ukazuju na veliku vjerojatnost teške trožilne bolesti ili bolesti glavnog debla lijeve koronarne arterije, a bolesnik je spreman podvrći se revaskularizaciji. Općenito, stoga, najnovije smjernice AHA/ACC nisu strogo definirane kao ranije smjernice NICE, možda dijelom i zato što je stavljen i manji naglasak na odnos troškovne učinkovitosti preporuka.

LIJEČENJE STABILNE KORONARNE BOLESTI SRCA

U novim NICE smjernicama[14] preporučeno je početno liječenje kratkodjelujućim nitratima i beta-blokatorom i/ili blokatorom kalcijevog kanala za kontrolu angiozinih tegoba uz acetilsalicilatnu kiselinu (ASK) i statin za sekundarnu prevenciju. Naglašene su i mjere koje se odnose na životne navike. Za bolesnike koji i dalje imaju angiozne tegobe preporučuje se koronarografija uz eventalnu revaskularizaciju, dok se dodatno medikamentozno liječenje za suzbijanje angine (dugodjelujući nitrati ili jedan od novijih lijekova) preporučuje samo bolesnicima koji su procijenjeni nepodobni za revaskularizaciju. Način revaskularizacije (perkutana koronarna intervencija (PCI) ili aortokoronarne premosnice (CABG) se određuje na multidisiplinarnom timu, a ta preporuka je također naglašena i u smjernicama europskog udruženja,[15] imajući na umu povoljniji učinak CABG u bolesnika s kompleksnom višežilnom koronarnom bolesti i bolesti debla lijeve koronarne arterije, a posebno kod dijabetičara.[16] Za simptomatske bolesnike koji su prihvatljivo kontrolirani farmakološkom terapijom, u smjernicama se preporučuje prikaz i rasprava o potencijalnom prognostičkom poboljšanju s CABG. Onim bolesnicima koji bi naknadno pristali na CABG, mogla bi se ponuditi dijagnostička koronarografija radi isključenja kompleksne višežilne bolesti i bolesti glavnog debla lijeve koronarne arterije o kojoj je izviješteno u meta-analizi kod čak 36% (18,5-48,8%) slučajeva stabilne koronarne bolesti odabranih za kateterizaciju srca.[17]

which 13,293 Caucasian and 2,120 S Asians consented to mortality follow-up.[10] Physical inactivity was more frequent in S Asians compared with Caucasians (47% vs 28%) and explained >20% of their excess CHD mortality. Certainly, the emerging consensus is that the excess CHD mortality among UK S Asians is driven almost entirely by their increased susceptibility to disease and not by increased case-fatality rates.[11]

DIAGNOSIS OF STABLE CORONARY ARTERY DISEASE

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

MANAGEMENT OF STABLE CORONARY ARTERY DISEASE

The recent NICE guideline[14] recommended initial treatment with a short-acting nitrate and a beta-blocker and/or a calcium channel blocker for control of angina plus aspirin and a statin for secondary prevention. Lifestyle measures were also emphasised. For patients with continuing symptoms cardiac catheterisation with a view to revascularization was recommended, additional antianginal treatment (long-acting nitrates or one of the newer agents) only being indicated for patients unsuitable for revascularisation. It was further recommended that the mode of revascularisation (percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG)) should best be determined by a multidisciplinary group, a recommendation that has also been emphasised by European guideline groups,[15] bearing in mind the potential for prognostic benefit from CABG in patients with complex multivessel and left main stem disease, particularly those with diabetes.[16] For patients with symptoms adequately controlled with medical treatment, the guideline recommended discussion of the potential for prognostic improvement with CABG. Those patients prepared to proceed to CABG might then be offered diagnostic cardiac catheterisation to rule out complex multivessel and left main stem disease, which a recent meta-analysis reported in as many as 36% (18.5-48.8%) of cases of stable coronary disease selected for cardiac catheterization.[17]

SEKUNDARNA PREVENCIJA STABILNE KORONARNE BOLESTI SRCA

Dodatni prostor za poboljšanje sekundarne prevencije u bolesnika sa stabilnom KBS je naglašen u dva nedavna izvješća. U multinacionalnom registru REACH, 20.588 simptomatskih bolesnika su analizirani su radi "dobre kontrole" kardiovaskularnih čimbenika rizika, koja je definirana kao tri do pet čimbenika: sistolički arterijski tlak <140 mmHg, dijastolički arterijski tlak <90 mmHg, glikemija natašte <110 mg/dl, ukupni kolesterol <5,17 mmol/L, nepušenje.[18] Samo 59,4% imalo je dobru kontrolu čimbenika rizika na početku, a to je bilo povezano s nižim mortalitetom (OR 0,89; 95% CI 0,79-0,99) u 36. mjesecu, u usporedbi s lošom kontrolom čimbenika. U britanskom istraživanju ASPIRE-2-PREVENT, 676 bolesnika s KBS (25,6% žena) su imali sljedeću učestalost glavnih čimbenika rizika: pušenje 14,1%, pretilost 38%, tjelesna neaktivnost 83,3%, arterijski tlak ≥130/80 mmHg, ukupni kolesterol ≥4 mmol/l i dijabetes 17,8% što je autore navelo na zaključak da postoji značajan potencijal za smanjenje kardiovaskularnog rizika kod ovih bolesnika, a time i poboljšanje prognoze.[19]

Klopidogrel

Dostupnost jeftinog generičkih klopidogrela je potaknuo reviziju NICE-a u smislu njegove isplativosti te je preporuka dovela do istiskivanja ASK u pojedinim visokorizičnim skupinama, odnosno kod bolesnika s višestrukom vaskularnom bolesti, perifernom vaskularnom bolesti i infarktom miokarda.[20] Međutim, klopidogrel se metabolizira enzimima u sustavu jetrenog citokroma P450 (CYP), a promjenjivost u antiagregacijskom djelovanju se može pojaviti zbog djelovanja ovih enzima te se na nju utječe uobičajenim genetskim varijacijama, kao i velikim brojem često korištenih lijekova. U nekoliko studija se navodi smanjenje aktivacije alela u CYP2C[19] što za posljedicu ima smanjenu aktivaciju klopidogrela[21] i umjerno sniženje antiagregacijskog djelovanja,[22] što je povezano s povećanim rizikom od kardiovaskularnih bolesti kod nekih meta-analiza.[23] Obrnuto, pojačana aktivacija alela je povezano sa smanjenjem kardiovaskularnog rizika kod bolesnika liječenih klopidogrelom.[24] Nedavna meta-analiza se međutim nije osvrnula na tendenciju malih studija, koje mogu biti opterećene biasom o načinu kako genetske varijante utječu na kliničke ishode, dok u većim studijama terapije klopidogrelom s ≥200 krajnih ishoda nije nađen učinak smanjene aktivacije alela na kardiovaskularni rizik.[25] Trenutno se dakle čini da nema niti jednog uvjerljivog pokazatelja za genetsko testiranje pri vođenju terapije klopidogrelom, iako je ova tema i dalje predmet stalnih rasprava. Također se raspravlja o interakciji klopidogrela s nekim često korištenim lijekovima, osobito inhibitorima protonske pumpe (IPP) i amlodipinom. Nedavnom metaanalizom studija IPP u bolesnika liječenih klopidogrelom nađen je jasan dokaz smanjene aktivnosti trombocita, ali iako se čini da je na kliničke ishode interakcija negativno utjecala, autori su pozvali na oprezno tumačenje, ističući heterogenost uzrokovane retrospektivnim studijama. Kada je analiza ograničena na prospektivne studije IPP i klopidogrela, štetne kliničke posljedice se više ne bi mogle dokazati (OR 1,13 (0,98-1,30)).[26] Slično tome, klinički učinak amlodipina na reakciju na klopidogrel i dalje ostaje nejasan. Dakako, postoje dokazi o interakciji, a u jednoj studiji od 1.258 bolesnika koji su primali klopidogrel, primjena amlodipina je povezano s višom reaktivnošću trombocita u tijeku terapije samo u onih bolesnika sa smanjenom aktivacijom genotipa P450 (CYP)

SECONDARY PREVENTION OF STABLE CORONARY DISEASE

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

Clopidogrel

The availability of low-cost generic clopidogrel prompted a NICE review of its cost effectiveness which recommended it should now supersede aspirin in certain high-risk groups, namely patients with multivascular disease, peripheral vascular disease and myocardial infarction.[20] However, clopidogrel is metabolised by enzymes in the hepatic cytochrome P450 (CYP) system, and variability in its antiplatelet activity may occur because the activity of these enzymes is influenced by common genetic variations, and also by a number of commonly used drugs. Several studies have reported loss-of-function alleles in CYP2C[19] that result in reduced activation of clopidogrel[21] and a modest lowering of antiplatelet activity[22] which have been associated with an increased risk of cardiovascular events in some meta-analyses.[23] Conversely, gain-of-function alleles have been associated with reduced cardiovascular risk among clopidogrel-treated patients.[24] A recent meta-analysis, however, has commented on the tendency of small studies to bias conclusions about the way genetic variants influence clinical outcomes, and in larger studies of clopidogrel therapy with ≥200 outcome events found no effect of loss-of-function alleles on cardiovascular risk.[25] At present, therefore, there seems to be no compelling indication for genetic testing to guide clopidogrel treatment although the topic remains a subject of ongoing debate. Also debated is the interaction of clopidogrel with some commonly used drugs, particularly proton pump inhibitors (PPI) and amlodipine. A recent meta-analysis of studies of PPIs in patients treated with clopidogrel found clear evidence of reduced platelet activity but although clinical outcomes appeared adversely affected by the interaction, the authors urged cautious interpretation, pointing out the heterogeneity caused by retrospective studies. When analysis was restricted to prospective studies of PPIs and clopidogrel, adverse clinical consequences could no longer be demonstrated (OR 1.13 (0.98-1.30)).[26] Similarly, the clinical impact of amlodipine on responsiveness to clopidogrel remains uncertain. Certainly, there is evidence of interaction, and in one study of 1,258 patients receiving clopidogrel, amlodipine administration was associated with higher on-treatment platelet reactivity only in those patients with a loss-of-function P450 (CYP) genotype (249±83 vs 228±84 P2Y12

(249±83 naspram 228±84 P2Y12 reakcijskih jedinica), i to je bilo povezano s većom učestalošću kardiovaskularnih događaja (4,6% naspram 0,6%).[27] Međutim, u novijem randomiziranom istraživanju, funkcija trombocita u 98 bolesnika sa stabilnom KBS koji su uzimali klopidogrel je bila slična bez obzira na terapiju amlodipina.[28] Trenutno, dakle ne postoje smjernice za preporuku o istovremenom propisivanju ovih lijekova kod bolesnika koji uzimaju klopidogrel.

Statini, nijacin i inhibitori kolesteril-ester transfer proteina (CETP)

Prednosti statina za sekundarnu prevenciju kod bolesnika s stabilnom KBS su dobro utvrđene. Kardiovaskularni zajednički ishodi se smanjuju razmjerno stupnju smanjenja LDL-kolesterola, vjerojatno kao odgovor na stabilizaciji i regresiju ateromatoznog plaka. Kapacitet za regresiju plaka je nedavno potvrdilo i serijsko ispitivanje primjenom IVUS kod 1.039 bolesnika sa stabilnom KBS randomiziranih na rosuvatatin 40 mg dnevno ili atorvastatin 80 mg dnevno.[29] Volumen ateroma tijekom razdoblja praćenja od 2 godine se smanjio u prosjeku za oko 1% u obje skupine, više nego što se prethodno objavljeno s manje intenzivnim režimima statina. Međutim, dodatne kliničke koristi niacina sada nisu nedvosmisleno odbačene u istraživanju AIM-HIGH u kojem je 3.414 bolesnika sa stabilnom kardiovaskularnom bolešću koji uzimaju statine randomizirano za niacin (n = 1.718) ili placebo (n = 1.696).[30] Iako je niacin značajno povećao HDL-kolesterol i snizio trigliceride, razlike u primarnim zajedničkim ishodima (broj nepovoljnih koronarnih događaja, moždanih udara i revaskularizacije) su bili zanemarivi, i javili su se kod 16% bolesnika u svakoj skupini. Istraživanje je zaustavljeno nakon prosječnog praćenja od 3 godine, kada je postalo jasno da je terapija podizanja HDL s niacinom bila klinički nedjelotvorna. Sve nade za povišenje razine HDL su sada usmjerene prema CETP inhibitorima, unatoč problemima vezanim za sigurnost nakon istraživanja ILLUMINATE o torcetrapibu,[31] u kojem je liječenje bilo povezano s povećanom smrtnošću unatoč značajnim povišenjima HDL, a ostali inhibitori CETP sada ulaze u III fazu istraživanja. Nedavno randomizirano istraživanje dalcetrapiba u bolesnika s akutnim koronarnim sindromom je bilo razočaravajuće bez smanjenja rizika ponovljenih koronarnih događaja unatoč povećanju razina HDL od >30% u skupinama liječenja.[32] Učinkovitost i sigurnost istraživanja anacetrapiba u bolesnika sa visokim rizikom stabilne koronarne bolesti je bilo povoljno, iako nisu bili zajamčeni klinički ishodi,[33] a evacetrapib je sada uključen u nedavno istraživanje u kojem se prikazuje učinkovito podizanje HDL bez štetnih učinaka na arterijski tlak što je zabilježeno kod torcetrapiba i, u manjoj mjeri, dalcetrapiba.[34] Ostaje nepoznato hoće li bilo koji od ovih inhibitora CETP poboljšati kliničke ishode.

Novi lijekovi za snižavanje vrijednosti lipida u kliničkim studijama

Konvencionalne terapije snižavanja lipida čak i u kombinaciji sa LDL-aferezom su često nedovoljne za liječenje bolesnika prema ciljnim vrijednostima u smjernicama kod bolesnika s obiteljskom hiperkolesterolemijom (FH), autosomnom dominantnom poremećaju metabolizma lipida povezanog s ubrzanom KBS.[35] Postoji, prema tome, značajan interes za novim terapijama koje se trenutno istražuju, naročito lomitapid, oralni inhibitor mikrosomalnog transfer proteina i monoklonska antitijela protiv PCSK9. Faza II studije o lomitapi-

reaction units), and this was associated with a higher incidence of cardiovascular events (4.6% vs 0.6%).[27] However, in a more recent randomised trial, platelet function in 98 patients with stable coronary artery disease taking clopidogrel was similar regardless of amlodipine therapy.[28] At present, therefore, there is no guideline recommendation about concomitant prescription of these drugs in patients taking clopidogrel.

Statins, niacin and cholesteryl ester transfer protein (CETP) inhibitors

The benefits of statins for secondary prevention in patients with stable coronary artery disease are well established. Cardiovascular end-points are reduced in proportion to the degree of LDL-cholesterol reduction, probably in response to stabilisation and regression of atheromatous plaque. The capacity for plaque regression has recently been confirmed by serial IVUS examination in 1,039 patients with stable coronary disease randomised to rosuvastatin 40 mg daily or atorvastatin 80 mg daily.[29] Atheroma volume during the 2-year monitoring period decreased by an average of about 1% in both groups, more than previously reported with less intensive statin regimens. However, additional clinical benefits of niacin have now been unequivocally ruled out in the AIM-HIGH trial in which 3,414 patients with stable cardiovascular disease taking statins were randomised to receive niacin (n = 1,718) or placebo (n = 1,696).[30] Although niacin significantly increased HDL cholesterol and lowered triglycerides, differences in the primary endpoints (a composite of adverse coronary events, strokes and revascularisation) were negligible, occurring in 16% of patients in each group. The trial was stopped after an average follow-up of 3 years when it became clear HDL raising therapy with niacin was clinically ineffective. All hopes for HDL raising therapy are now invested in CETP inhibitors, and despite safety concerns following the ILLUMINATE trial of torcetrapib,[31] in which treatment was associated with increased mortality despite substantial HDL elevations, other CETP inhibitors are now entering phase III trials. A recent randomised trial of dalcetrapib in patients with acute coronary syndromes was disappointing with no reduction in the risk of recurrent coronary events despite a >30% increase in HDL levels in the treatment group.[32] An efficacy and safety trial of anacetrapib in patients with, or at high risk of, stable coronary disease was favourable, although not powered for clinical outcomes[33], and evacetrapib has now entered the arena with a recent study showing effective HDL raising without the adverse effects on blood pressure seen with torcetrapib and, to a lesser extent, dalcetrapib.[34] Whether any of these CETP inhibitors will improve clinical outcomes, however, remains unknown.

Novel lipid-lowering drugs in clinical translation

Conventional lipid-lowering therapies, even when combined with LDL-apheresis, are often insufficient to treat to guideline targets patients with familial hypercholesterolaemia (FH), an autosomal dominant disorder of lipid metabolism associated with accelerated coronary disease.[35] There is, therefore, considerable interest in novel therapies currently under investigation, particularly lomitapide, an oral inhibitor of microsomal transfer protein and monoclonal antibodies against PCSK9. A phase II study of lomitapide in homozy-

du u homozigotnom FH je pokazala smanjenje od 50% LDL-kolesterola i, iako su gastrointestinalne nuspojave bile česte, korisna uloga za lijek se činila vjerojatnom kod ovih homozigotnih bolesnika.[36] Inhibitori PCSK9 su također doveli do 50-60% smanjenja vrijednosti LDL-kolesterola u kliničkim studijama kada se dodaju statinima i ezetimibima, ali za razliku od lomitapida, vjerojatno su uglavnom učinkoviti kod heterozigotnih FH, jer oni djeluju preko intereferencije s LDL receptorima, koji su disfunkcionalni ili u potpunosti odsutni kod homozigota.[37,38] Očekuje se da će primjena tih novih lijekova omogućiti većini bolesnika s FH postizanje ciljnih koncentracija LDL kolesterola. Važna komponenta zbrinjavanja FH uključuje utvrđivanje ostalih zahvaćenih članova obitelji, a kaskadni probir koristeći gensko testiranje se pokazalo troškovno učinkovitim.[39] Međutim, nedavni dokazi upućuju da poligenski poremećaji čine značajan dio slučajeva FH,[40] a time će se učinkovitost kaskadnog probira ograničiti na rođake mutacijskih-pozitivnih (monogenskih) slučajeva. Kod drugih bolesnika sa razinama kolesterola koji je u skladu s genotipom FH, uobičajene primarne mjere zbrinjavanja[41] bi trebale ostati metoda izbora probira, barem zasada.

REVASKULARIZACIJA KOD STABILNE KORONARNE BOLESTI SRCA

Perkutana koronarna intervencija

Studija COURAGE je donijela obrat pokazavši da stentiranje koronarnih arterija u bolesnika sa stabilnom anginom ne pospješuje kardiovaskularne ishode u usporedbi s optimalnom farmakološkom terapijom (OMT), dok su koristi u pogledu kvalitete života bile kratkog trajanja.[42,43] Sada je dostupna metaanaliza u kojoj se uspoređuje najnovija medikamentozna terapija i PCI u osam randomiziranih istraživanja koja uključuju 7.229 bolesnika sa stabilnom KBS.[44] Ponovno, kardiovaskularni ishodi između skupina su bili slični tijekom praćenja od prosječno 4,3 godine, bez značajne kliničke koristi za PCI, rizika od smrti (8,9% naspram 9,1%) i nefatalnog infarkta miokarda (8,9% naspram 8,1%) što je gotovo istovjetno medikamentoznoj terapiji, dok su razlike u neplaniranoj revaskularizaciji (21,4% naspram 30,7%) i perzistentnoj angini (29% naspram 33%) bile male i neznačajne. Podaci podržavaju nedavne preporuke iz smjernica za liječenje stabilne angine (vidi gore) te su korišteni kao poziv za preispitanje mišljenja liječnicima koji i dalje preporučaju PCI bolesnicima koji se ne liječe pomoću OMT.[45] Međutim, studija FAME-II je sada omogućila potporu ranom intervencijskom pristupu u randomiziranoj usporedbi OMT i PCI uz uporabu DES i intervenciju vođenu nalazom frakcije pričuvnog protoka (FFR).[46] Studija je zaustavljena 17 mjeseci prije nego što je planirano, jer se primarni zbirni ishod (smrtnost od svih uzroka, nefatalni infarkt miokarda, hitna revaskularizacija) dogodio u 4,3% u skupini na PCI u usporedbi s 12,7% u skupini na OMT. Ublažavanje angine također je bilo učinkovitije u skupini liječenoj primjenom PCI. Metoda PCI vođena FFR-om postala je već preporučena strategija kod stabilne KBS, ali neki smatraju da je to prerano za zaključke.[47] Tako je razlika u učinku liječenja u studiji FAME-II proizašla isključivo smanjenjem hitne revaskularizacije (49 samo u OMT skupini; 7 u FFR-PCI skupini (HR = 0,13; 95% CI 0,06-0,30), dok su 33 smrti i nefatalni infarkti miokarda bili ravnomjerno raspoređeni između skupina. Štoviše, većina bolesnika koji su podvrgnuti žurnoj revaskularizaciji nisu imali objektivne nalaze visoko rizične ishemije ili porasta biomarkera te se time postavlja pitanje "bias-a" u odabiru bolegous FH showed a 50% reduction in LDL-cholesterol and, although gastrointestinal side effects were common, a useful role for the drug seems likely in these homozygous patients.[36] PCSK9 inhibitors have also produced 50-60% reductions in LDL-cholesterol values in clinical studies when added to statins and ezetimibe, but unlike lomitapide, are probably mainly effective in heterozygotic FH because they act through interference with LDL receptors which are dysfunctional or completely absent in homozygotes.[37,38] The expectation is that application of these new drugs will allow most patients with FH to achieve target concentrations of LDL cholesterol. An important component of FH management involves identification of other affected family members, and cascade screening using genetic testing has been reported as cost effective.[39] However, recent evidence suggests that polygenic disorders account for an appreciable proportion of FH cases,[40] and this will limit the effectiveness of cascade screening to relatives of mutation-positive (monogenic) cases. In other patients, with cholesterol levels consistent with an FH genotype, more conventional primary care strategies[41] should remain the screening tool of choice, at least for the time being.

REVASCULARISATION IN STABLE CAD

Percutaneous coronary intervention

The COURAGE trial was a game-changer, showing that coronary stenting in patients with stable angina did not improve cardiovascular outcomes compared with optimal medical therapy (OMT) while quality-of-life benefits were short-lived.[42,43] Now available is a meta-analysis comparing contemporary medical therapy and PCI in eight randomised trials involving 7,229 patients with stable CAD.[44] Again, cardiovascular outcomes between the groups were similar during follow-up for an average 4.3 years with no significant clinical benefit for PCI, risks of death (8.9% vs 9.1%) and non-fatal MI (8.9% vs 8.1%) being nearly identical with medical therapy, while differences in unplanned revascularisation (21.4% vs 30.7%) and persistent angina (29% vs 33%) were small and insignificant. The data support recent guideline recommendations for treatment of stable angina (see above), and have been used to challenge those clinicians who continue to offer PCI to patients not receiving OMT.[45] However, FAME-II has now provided some support for an early interventional approach in a randomised comparison of OMT and PCI using drug-eluting stents guided by fractional flow reserve (FFR).[46] The study was stopped 17 months earlier than planned because the composite endpoint (all-cause mortality, non-fatal MI, urgent revascularisation) occurred in 4.3% of the PCI group compared with 12.7% of the non-PCI (OMT) group. Relief of angina was also more effective in the PCI group. Already, PCI guided by FFR has become a recommended strategy in stable coronary artery disease but some feel this is premature.[47] Thus, the treatment difference in FAME-II was driven solely by a reduction in urgent revascularisation (49 in the OMT alone group; 7 in the FFR-PCI group (HR = 0.13, 95% CI 0.06-0.30), while the 33 deaths and non-fatal MIs were distributed fairly evenly between the groups. Moreover, the majority of patients undergoing 'urgent' revascularisation lacked objective findings of high-risk ischaemia or threshold biomarker elevations, raising concerns of biased selection of patients for invasive management during follow-up. Nevertheless, the argument in favour of interventional management as an initial strategy in stable angina has undoubtedly been strengthened by FAME-II, but

snika za invazivni pristup tijekom razdoblja praćenja. Ipak, dokazi u korist intervencijskog zbrinjavanja kao početne strategije kod stabilne angine nesumnjivo su se osnažili u studiji FAME-II, no, konačni odgovori na temu će možda morati pričekati rezultate istraživanja ISCHEMIA, u kojem se uspoređuju učinci revaskularizacije (PCI ili CABG) u kombinaciji s OMT, samo s OMT na kardiovaskularnu smrtnost ili infarkt miokarda kod bolesnika sa stabilnom KBS i objektivnim dokazima ishemije miokarda.

Aortokoronarno premoštenje

Aktualne američke smjernice[48] podržavaju preporuka NICE smjernica o multidisciplinarnom timskom pristupu pri donošenju odluka o revaskularizaciji kod bolesnika s kompleksnom KBS, potičući primjenu SYNTAX i drugih alata/ljestvica za donošenje odgovarajuće odluke.[49] Mogućnost za CABG u usporedbi s PCI za poboljšanje prognoze kod bolesnika s bolešću debla lijeve koronarne arterije i višežilne KBS je podržana u nedavno objavljenim kohortnim studijama,[50,51] a sada su dostupni podaci petogodišnjeg praćenja iz studije SYNTAX u kojoj su glavni nepovoljni srčani i cerebrovaskularni događaji (MACCE) bili 26,9% u skupini na CABG i 37,3% u skupini na PCI, uglavnom zahvaljujući nižim stopama nefatalnog infarkta miokarda i ponovljene revaskularizacije za CABG, bez značajne razlike u smrtnosti od svih uzroka i moždanog udara u usporedbi s PCI.[52] Prednosti CABG su posebno bile vidljive kod bolesnika sa srednjim i visokim rezultatima primjene SYNTAX ljestvice, bez da postoji značajna razlika u ishodima među strategijama revaskularizacije za bolesnike s niskim rezultatima SYNTAX ljestvice. Sva pitanja o strategiji izbora revaskularizacije kod bolesnika s dijabetesom i višežilnom KBS sada su odgovorena u studiji FREEDOM u kojoj je randomizirano 1.900 bolesnika na OMT za PCI sa DES ili CABG.[53] Nakon prosječnog praćenja od 3,8 godina, primarni ishod, koji se sastoji od smrti od bilo kojeg uzroka, nefatalnog infarkta miokarda, odnosno nefatalnog moždanog udara, dogodio se u 26,6% PCI skupine i 18,7% u skupini CABG. Autori su zaključili da je CABG superioran u odnosu na PCI u bolesnika s dijabetesom i višežilnom KBS. Odluka o strategiji izbora revaskularizacije debla lijeve koronarne arterije manje je određena, pri čemu su SYNTAX istražitelji izvijestili o sličnim ishodima za PCI i CABG, a rezultat je u skladu s ostalim suvremenim studijama u kojima se ugradnja stenta smatra razumnom strategijom kod dobro odabranih slučajeva, iako je potreba za ponovnom revaskularizacijom gotovo uvijek veća nego kod CABG.[54,55]

Kirurška tehnika se u zadnje vrijeme počela detaljno istraživati. Zabrinutosti zbog mogućih nuspojava endoskopske metode vađenja vene safene naspram otvorenog kirurškog zahvata uklanjanja vene safene se u velikoj mjeri temelje na nerandomiziranoj kohortnoj studiji od 1.817 bolesnika kod kojih je učestalost neuspjeha presađivanja vene u 1. godini bili 47% naspram 38%, a stope smrti, infarkta miokarda ili revaskularizacije u 3. godini su bile 20,2% naspram 17,4 % za endoskopsku naspram otvorene metode vađenja vene safene.[56] Zbog toga se NICE smjernice preporučile oprez u korištenju endoskopske tehnike,[57] ali ta zabrinutost se sada smanjuje zbog rezultata dviju velikih kohortnih studija. U američkoj studiji kod 235.394 Medicare bolesnika s CABG stope smrtnosti iz nacionalne baze podataka su bile slične bez obzira na tehniku vađenja, dok su stope komplikacija lokacije vađenja bile niže za endoskopsku tehniku.[58] Britanska studija sa 4.702 bolesnika s CABG je izvijestila o sličnim rezultatima, bez razlika u bolničkoj smrtnosti (0.,9% vs 1,1%, p = 0.71 i srednjoročnoj smrtnosti (HR 1,04; 95% CI 0.65-

final answers to the debate may have to await the findings of the ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA Trial; ClinicalTrials.gov number, NCT 01471522), comparing effects of revascularisation (PCI or CABG) combined with OMT, with OMT alone on cardiovascular death, or MI in patients with stable CAD, and objective evidence of myocardial ischaemia.

Coronary artery bypass surgery

Updated US guidelines[48] have endorsed the NICE recommendation of a multidisciplinary team approach to adjudicating revascularisation decisions in patients with complex coronary disease, encouraging application of SYNTAX and other scoring systems in arriving at an appropriate decision.[49] The potential for CABG compared with PCI to improve prognosis in patients with left main and multivessel CAD is supported by recent cohort studies,[50,51] and now available are the 5-year follow-up data from SYNTAX in which major adverse cardiac and cerebrovascular events (MACCE) were 26.9% in the CABG group and 37.3% in the PCI group, driven largely by lower rates of non-fatal myocardial infarction and repeat revascularisation for CABG, with no significant difference in all-cause mortality and stroke compared with PCI.[52] The benefits of CABG were particularly evident in patients with intermediate and high SYNTAX scores, there being no significant difference in outcomes between revascularisation strategies for patients with low SYNTAX scores. Any question about the preferred revascularisation strategy in patients with diabetes and multivessel coronary artery disease has now been answered by the FREEDOM TRIAL which randomised 1,900 patients on OMT to either PCI with drug-eluting stents or CABG.[53] After a median follow-up of 3.8 years, the primary outcome, a composite of death from any cause, non-fatal myocardial infarction, or non-fatal stroke, occurred in 26.6% of the PCI group and 18.7% of the CABG group. The authors concluded that CABG is superior to PCI in patients with diabetes and multivessel disease. There is less certainty about the preferred revascularisation strategy in left main coronary disease, the SYNTAX investigators reporting similar outcomes for PCI and CABG, a finding consistent with other contemporary studies that identify stenting as a reasonable strategy in appropriately selected cases, even though the need for repeat revascularisation is almost invariably higher compared with CABG.[54,55]

Surgical technique has come under considerable scrutiny recently. Concerns about the potential adverse effects of endoscopic versus open saphenous vein harvesting have been based largely on a non-randomised cohort study of 1,817 patients in whom rates of vein graft failure at 1 year were 47% vs 38%, and rates of death, myocardial infarction or revascularisation at 3 years were 20.2% vs 17.4% for endoscopic versus open saphenous vein harvesting.[56] This led NICE to recommend caution in use of the endoscopic technique,[57] but such concerns have now been allayed by the results of two large cohort studies. In the US study of 235,394 Medicare CABG patients in the Society of Thoracic Surgeons (STS), national database mortality rates were similar regardless of harvesting technique, while rates of harvest site complications were lower for the endoscopic technique.[58] A UK study of 4,702 CABG patients reported similar findings with no differences in in-hospital mortality (0.9% vs 1.1%, p = 0.71) or midterm mortality (HR 1.04; 95% CI 0.65-1.66) for endoscopic versus open vein harvesting.[59]

1.66) za endoskopsku u odnosu na otvorenu metodu vađenja vene.[59]

Također se iscrpno istražuju relativne prednosti zahvata kardiokirurške revaskularizacije bez ili uz potporu stroja za vantjelesnu cirkulaciju. Svaki ima svoje zagovornike,[60,61] ali rezultati randomiziranih istraživanja nisu uspjeli pokazati jasnu prednost CABG bez potpore stroja za vantjelesnu cirkulaciju, pri čemu su trogodišnji rezultati studije Best Bypass Surgery Trial pokazali da nema značajne razlike u primarnom složenom ishodu MACCE u odnosu na CABG s kardiopulmonalnim premoštenjem, nego tendenciju veće smrtnosti.[62] Time se barem djelomično mogu prikazati razlike u stopama prohodnosti favorizirajući postupke korištenja kardiopulmonalnog premoštenja, pri čemu je istraživanje ROOBY objavilo stope od 91,4% naspram 85,8% za arterijske transplantate i 80,4% naspram 72,7% za transplantate vene safene kod bolesnika kod kojih se primjenjuje postupak korištenja kardiopulmonalnog premoštenja u odnosu na bolesnike kod kojih se ne primjenjuje kardiopulmonalno premoštenje.[63] Osobito je bio razočaravajući neuspjeh operacije bez korištenja kardiopulmonalnog premoštenja za smanjenje cerebralne ozljede, ali randomizirana usporedba minimalne (MECC) u odnosu na konvencionalnu (CECC) izvantjelesnu cirkulaciju u 64 bolesnika podvrgnutih CABG je više obećavajuća.[64] MECC je povezana s poboljšanom opskrbom mozga kisikom tijekom operacije, a neurokognitivni rezultat u 3 mjeseca je bio bolji u usporedbi s CECC.

ISHEMIJSKO PREDKONDICIRANJE UDALJENIH ORGANA ILI TKIVA ZA LIJEČENJE STABILNE KORONARNE BOLESTI SRCA

Zagovornici smatraju ishemijsko predkondiciranje udaljenih organa (RIPC) korisnim i jeftinim načinom za poboljšanje ishoda u širokom nizu kardiovaskularnih bolesti. Za njih je stoga frustrirajući neuspjeh proboja tehnike u kliničku praksu, uz proturječna izvješća o njegovoj učinkovitosti, a neuvjerljivost mehanizma učinka potkopava povjerenje u kliničku korisnost RIPC. Neka novija randomizirana istraživanja su bila povoljna, u jednom se izvijestilo o zaštiti od kontrastom inducirane nefropatije tijekom kateterizacije srca,[65] a drugom o smanjenju oštećenja miokarda tijekom operacije srčanih zalistaka.[66] Možda je najpovoljnije bilo randomizirano istraživanje predbolničkog RIPC kod 333 bolesnika sa STEMI koji subili liječeni primarnom PCI.[67] Skupina s RIPC je pokazala značajno poboljšanje u indeksu spašavanja miokarda u usporedbi s skupinom bez RIPC (0,75 naspram 0,55), iako istraživanje nije uključilo dovoljno ispitanika za praćenje koronarnih događajia. Nasuprot toga se mora prikazati negativno istraživanje RIPC u skupini bolesnika podvrgnutih CABG,[68] ali je malo vjerojatno da će to biti posljednja riječ, jer se već metaanalizom od devet studija koje su uključivale 704 bolesnika zaključilo da RIPC značajno smanjuje otpuštanje troponina tijekom CABG.[69] Studije u kojima se pratio mehanizam djelovanja uključuju križnu studiju u bolesnika sa stabilnom KBS, a u toj studiji RIPC je smanjio djelovanje trombocita tijekom testiranja pod opterećenjem, bez zaštite od ishemijskih elektrokardiografskih promjena.[70] U drugoj studiji u kojoj se koristila venska pletizmografija krvotoka podlaktice kod zdravih dobrovoljaca, RIPC je štitio od oštećenja vazomotorne funkcije endotela, koja nastaje pri ishemiji.[71] Međutim, na tu zaštitu nije utjecala infuzija antagonista bradikinin B2 receptora, navodeći autore na zaključak da bradikinin nije medijator RIPC.

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

REMOTE ISCHAEMIC PRECONDITIONING FOR TREATMENT OF STABLE CORONARY DISEASE

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

PROGNOSTIC BIOMARKERS IN STABLE CAD

Circulating biomarkers

Interest in circulating cardiovascular biomarkers has never been higher, and methodological papers have been developed to alert researchers to the standards necessary for proper evaluation of their prognostic utility.[72,73] However, a systematic review of 83 CRP studies was critical of their ge-

PROGNOSTIČKI BIOMARKERI KOD STABILNE KORONARNE BOLESTI SRCA

Biomarkeri u cirkulaciji

Interes za biomarkere u kardiovaskularnoj cirkulaciji nikada nije bio veći, a metodološki radovi su izrađeni kako bi upozorili istraživače o standardima potrebnim za pravilno vrednovanje njihove prognostičke koristi.[72,73] Međutim, sistematski pregledni članak o 83 CRP studija je bio kritičan prema njihovoj općoj kvaliteti te se zaključilo da više vrsta pristranosti u izvješćivanju i objavama čine važnost bile koje veze između CRP i prognoze među bolesnicima s stabilnom KBS dovoljno neizvjesnom da se ne mogu dati nikakve preporuke kliničke prakse.[74] Isti autori su bili jednako kritični prema 19 BNP studijama u bolesnika sa stabilnom KBS, pri čemu su izvijestili da su klinički korisne mjere za predviđanje i diskriminaciju uglavnom bile nedostupne te zaključili da je nije jasno dokazana nepristrana veza BNP s prognozom kod stabilne KBS.[75] Dostupnošću visokoosjetljivih reagenasa obnovljen je interes za troponine kao markera rizika kod stabilne KBS, pri čemu američka studija od 984 bolesnika u Heart and Soul Study navodi da je svako udvostručenje hs-cTnI razine povezano s 37% višom stopom kardiovaskularnih događaja.[76] U međuvremenu istraživači PEACE studije su objavili da je među 3.623 bolesnika sa stabilnom KBS hs-cTNI neovisno povezan s kardiovaskularnom smrću ili zatajivanjem srca (HR 1,88 (1,33-2,66; p <0,001)), a veza s nefatalnim infarktom miokarda je bila slabija (1,03-2,01; p = 0,031).[77] Dokazi iz CTCA upućuju na to da je klinički nezamjetna ruptura nekalcificiranog plaka s naknadnom mikroembolizacijom vjerojatno patofiziološki mehanizam povišenja troponina,[78] ali je još uvijek prerano procijeniti da li će imati kliničku ulogu u prognostičkoj procjeni stabilne KBS. Isto vrijedi i za dio proadrenomedulina iz srednje regije i drugih biomarkera koji se trenutno istražuju.[79]

Vaskularni biomarkeri

Debljina intime-medije karotidnih arterija (cIMT) je utvrđena kao prediktor kardiovaskularnih događaja u općoj populaciji, a slabije u bolesnika sa stabilnom KBS.[80] Njegova prediktivna vrijednost se može povećati dodatnim razmatranjem veličine karotidnog plaka omogućavajući dobivanja "ukupnog zbroja opterećenja" koji je bio prikazan od strane kineskih istražitelja radi poboljšanja predviđanja petogodišnjeg rizika od kardiovaskularnih primarnih ishoda u usporedbi sa samim cIMT.[81] Dakako, vrijednost samog cIMT za predviđanje kardiovaskularnog rizika u općoj populaciji je pod znakom pitanja nakon velike metaanalize podataka na razini sudionika kod 45.828 osoba u kojoj cIMT nije dodao gotovo ništa ocjeni rizika po Framinghamskoj ljestvici.[82] Drugom metaanalizom podataka na razini sudionika su postavljena ostala pitanja, a koja je uključivala 36.984 ljudi koji su praćeni u prosjeku od 7 godina.[83] Istraživači su pokazali da nema povezanosti između progresije cIMT i rizika od kardiovaskularnih događaja, pri čemu su preispitali valjanost korištenja promjene u cIMT kao surogata primarnih ishoda u istraživanjima kardiovaskularnog rizika.

Kalcij i paratiroidni hormon

Studije koje su ukazale na to da ljudi koji uzimaju kalcijeve dodatke mogu povećati svoj rizik od infarkta miokarda[84,85] su izazvale interes za serumski kalcij i njegov odnos prema kardiovaskularnim događajima u bolesnika s KBS. Nedavna

neral quality and concluded that multiple types of reporting bias, and publication bias, make the magnitude of any independent association between CRP and prognosis among patients with stable coronary disease sufficiently uncertain that no clinical practice recommendations can be made.[74] The same authors were equally critical of 19 BNP studies in patients with stable coronary disease, reporting that clinically useful measures of prediction and discrimination were generally unavailable, and concluding that the unbiased strength of association of BNP with prognosis in stable coronary disease is unclear.[75] The availability of high-sensitivity assays has seen renewed interest in troponins as markers of risk in stable coronary disease, a US study of 984 patients in the Heart and Soul Study reporting that each doubling in hs-cTnT level is associated with a 37% higher rate of cardiovascular events.[76] Meanwhile the PEACE investigators have reported that among 3,623 patients with stable coronary artery disease, hs-cTnI is independently associated with cardiovascular death or heart failure (HR 1.88 (1.33-2.66; p < 0.001)), the association with non-fatal myocardial infarction being weaker (1.03-2.01; p = 0.031).[77] Evidence from CTCA suggests that clinically silent rupture of non-calcified plaque with subsequent microembolisation is a likely pathophysiological mechanism of troponin elevation[78] but it is too soon to know whether it will have a clinical role in the prognostic assessment of stable coronary artery disease. The same applies to the mid-regional portion of proadrenomedullin and other biomarkers currently under investigation.[79]

Vascular biomarkers

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

Calcium and parathyroid hormone

Studies suggesting that people who take calcium supplements may be increasing their risk of myocardial infarction[84,85] have stimulated interest in serum calcium and its relation to cardiovascular events in patients with CHD. A recent study has confirmed that vitamin D, parathyroid hormone and calcium show association with cardiovascular risk factors in US adolescents,[86] and now we have data in 1,017 patients with stable coronary artery disease followed-up for a median of 8.1 years, suggesting that high calcium levels, but not high phosphate levels, might be associated with all-cause and cardiovascular mortality (HR 2.39-4.66).[87] The

studija je potvrdila da vitamin D, paratiroidni hormon i kalcij pokazuju povezanost s kardiovaskularnim čimbenicima rizika kod američkih adolescenata[86] i sada imamo podatke kod 1.017 bolesnika sa stabilnom KBS praćenih prosječno 8,1 godina, koji ukazuju na to da bi visoke razine kalcija, ali ne i visoke razine fosfata mogle biti povezane s ukupnom i kardiovaskularnom smrtnošću (HR 2,39 do 4,66).[87] Mehanizam ove povezanosti je nejasan, ali dokaz slične povezanosti visokog paratireoidnog hormona i kardiovaskularne smrtnosti u istoj kohorti može upućivati na mobilizaciju kalcija iz kostiju kao uzročno-posljedični put djelovanja.[88]

mechanism of this association is unclear, but the demonstration in the same cohort of a similar association between high parathyroid hormone and cardiovascular mortality may implicate calcium mobilisation from bone on the causal pathway.[88]

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*Address for correspondence: NIHR Biomedical Research Unit, Barts and the London School of Medicine and Dentistry, London Chest Hospital, London E2 9JX, United Kingdom.

E-mail: adamtimmis@mac.com

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