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Pregledni članak | Review paper

Almanah 2011.: akutni koronarni sindrom.

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

Almanac 2011: acute coronary syndromes.

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

Charles Knight*, Adam D. 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

SAŽETAK: *Ovaj pregledni članak ističe najnovija dostignuća u epidemiologiji, dijagnozi, stratifikaciji rizika i liječenju akutnog koronarnog sindroma (AKS). Sama količina novih studija odražava robusno stanje globalnog kardiovaskularnog istraživanja, a cilj je prikazati rezultate koji su od interesa za kliničku praksu kardiologa.*

Učestalost i stope smrtnosti infarkta miokarda (IM) se smanjuju, što je vjerojatno posljedica promjena životnog stila, naročito prestanka pušenja, i poboljšanja farmakološkog i intervencijskog liječenja. Troponini i dalje ostaju u ključni za postavljanje dijagnoze, a novi testovi visoke osjetljivosti dodatno snižavaju pragove detekcije i poboljšavaju ishode. Dodatna dijagnostička vrijednost ostalih cirkulirajućih biomarkera ostaje nejasna, a za stratifikaciju rizika pokazali su se korisnim jednostavni klinički algoritmi, poput GRACE ljestice.

Primarna perkutana koronarna intervencija (PCI) s minimalnom odgodom liječenja predstavlja najučinkovitiju strategiju reperfuzije kod akutnog infarkta miokarda s ST elevacijom (STEMI). Radijalni pristup je povezan s manjom učestalosti krvarenja od femoralnog pristupa, no ishodi se čine identičnima. Manualna trombektomija ograničava distalnu embolizaciju i veličinu infarkta, dok stentovi koji luče lijek smanjuju potrebu za daljnjim postupcima revaskularizacije. Lezije koje nisu vodeće se najbolje rješavaju elektivno, kao dogovorni postupak, po učinjenoj primarnoj PCI. Razvoj antitrombotskih i antiagregacijskih lijekova za primjenu kod primarne PCI se i dalje nastavlja, uz nove indikacije za fondaparinuks i bivalirudin te inhibitore glikoproteina IIb/IIIa. Ako primarna PCI nije dostupna na vrijeme, fibrinolitičko liječenje preostaje kao opcija, no strategija rane angiografske procjene preporuča se za sve pacijente.

Infarkt miokarda bez elevacije ST segmenta (NSTEMI) je sada dominantan fenotip i ishodi nakon akutne faze su znatno lošiji nego za STEMI. Mnogi pacijenti s NSTEMI ostaju suboptimalno liječeni te postoji mnogo novih članaka koji pokušavaju definirati najučinkovitiju antitrombotsku i antiagregacionu terapiju za ovu skupinu pacijenata. Koristi od ranog invazivnog liječenja za većinu pacijenata nisu sporne, no optimalno vrijeme zahvata i dalje ostaje neriješeno.

Kardiološka rehabilitacija se preporuča kod svih pacijenata s akutnim IM, no učestalost uključivanja u program je i dalje razočaravajuća. Kućni programi su učinkoviti i mogu biti prihvatljiviji za mnoge pacijente. Dokazi za korist od promjene životnog stila i farmakoterapije za sekundarnu prevenciju

SUMMARY: *This overview highlights some recent advances in the epidemiology, diagnosis, risk stratification and treatment of acute coronary syndromes. The sheer volume of new studies reflects the robust state of global cardiovascular research but the focus here is on findings that are of most interest to the practising cardiologist.*

Incidence and mortality rates for myocardial infarction are in decline, probably owing to a combination of lifestyle changes, particularly smoking cessation, and improved pharmacological and interventional treatment. Troponins remain central for diagnosis and new high-sensitivity assays are further lowering detection thresholds and improving outcomes. The incremental diagnostic value of other circulating biomarkers remains unclear and for risk stratification simple clinical algorithms such as the GRACE score have proved more useful.

Primary percutaneous coronary intervention (PCI) with minimal treatment delay is the most effective reperfusion strategy in ST elevation myocardial infarction (STEMI). Radial access is associated with less bleeding than with the femoral approach, but outcomes appear similar. Manual thrombectomy limits distal embolisation and infarct size while drug-eluting stents reduce the need for further revascularisation procedures. Non-culprit disease is best dealt with electively as a staged procedure after primary PCI has been completed. The development of antithrombotic and antiplatelet regimens for primary PCI continues to evolve, with new indications for fondaparinux and bivalirudin as well as small-molecule glycoprotein (GP)IIb/IIIa inhibitors. If timely primary PCI is unavailable, fibrinolytic treatment remains an option but a strategy of early angiographic assessment is recommended for all patients.

Non-ST segment elevation myocardial infarction (NSTEMI) is now the dominant phenotype and outcomes after the acute phase are significantly worse than for STEMI. Many patients with NSTEMI remain undertreated and there is a large body of recent work seeking to define the most effective antithrombotic and antiplatelet regimens for this group of patients. The benefits of early invasive treatment for most patients are not in dispute but optimal timing remains unresolved.

Cardiac rehabilitation is recommended for all patients with acute myocardial infarction but take-up rates are disappointing. Home-based programmes are effective and may be more acceptable for many patients. Evidence for the benefits of lifestyle modification and pharmacotherapy for secondary prevention continues to accumulate but the argument for omega-

su i dalje prisutni, dok je argumente za suplemente s omega-3 masnim kiselinama, nakon nedavnih negativnih studija, sada teško održati. Implantibilni kardioverter-defibrilatori štite pacijente s teškom formom IM od iznenadne smrti, no za primarnu prevenciju bi trebali biti temeljeni na mjerenjima ejekcijske frakcije lijeve klijetke kasnije (oko 40 dana) nakon početne kliničke slike, budući da njihova ranija implementacija ne pokazuje dobrobit u smanjenju smrtnosti.

KLJUČNE RIJEČI: *akutni koronarni sindrom, akutni infarkt miokarda, liječenje, smrtnost.*

3 fatty acid supplements is now hard to sustain following recent negative trials. Implantable cardioverter-defibrillators for patients with severe myocardial infarction protect against sudden death but for primary prevention should be based on left ventricular ejection fraction measurements late (around 40 days) after presentation, earlier deployment showing no mortality benefit.

KEYWORDS: *acute coronary syndrome, acute myocardial infarction, therapy, mortality.*

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Učestalost i pojavnost bolesti

Trendovi pojavnosti globalne epidemije koronarne bolesti srca variraju prema regiji, no u većini razvijenih zemalja smrtnost se smanjuje.[1] Promjene životnog stila doprinijele su ovom smanjenju — u najnovije vrijeme implementacija zabrane pušenja u mnogim zemljama već je doprinijela značajnom smanjenju akutnih koronarnih događaja.[2] Pušenje, značajan trombogeni stimulans, predstavlja glavnu determinantu za akutni infarkt miokarda s elevacijom ST-segmenta (STEMI)[3], a nedavna analiza od Kaiser Permanente iz Kalifornije (gdje se zakoni zabrane pušenja strogo provode) pokazala je 62% smanjenje učestalosti STEMI između 1999. i 2008. dok se učestalost akutnog infarkta miokarda bez elevacije ST-segmenta (NSTEMI) povećala za 30%.[4] Ukupno je registrirano smanjenja broja hospitalizacija akutnih koronarnih sindroma (AKS) unatoč snižavanju dijagnostičkog praga osjetljivih troponinskih biomarkera.[5] Ovo je popraćeno poboljšanjem 30-dnevne smrtnosti prilagođene dobi i spolu sa 10,5% u 1999. na 7,8% u 2008. godini. Povećana učestalost intervencijskog liječenja je nesumnjvo doprinijela poboljšanim ishodima, no paralelno poboljšanje liječenja stabilizacijom plaka visokim dozama statina su također značajni[6] budući se ranjivi fibroateromi tankog krova obično javljaju na mjestima koji su često udaljena od arterije povezane s infarktom miokarda (IM) i nisu povezani s težinom stenoze.[7,8]

Dijagnoza

Definicije za dijagnozu AKS su međunarodno dogovorene, a temelje se na mjerenju vrijednosti troponina uz prisutnost simptoma te elektrokardiografskih ili funkcijskih kriterija.[9]

Troponini

Nalaz promjene koncentracije troponina u prva 24 sata, uz bar jednu vrijednost iznad granice normale, ključna je za dijagnozu akutnog infarkta miokarda (AIM). Sad su dostupni visoko-osjetljivi testovi za troponin koji omogućavaju značajno snižavanje praga detekcije. Prethodna studija je procjenjivala četiri visoko-osjetljiva testa kod 718 pacijenata sa sumnjom na AKS, od kojih je 17% imalo AIM. Dijagnostički učinak je bio izvrstan, površina ispod ROC krivulje (mjera točnosti testa) je bila u rasponu od 0,95 do 0,96, u odnosu na 0,90 kod standardnih testova.[10] Kardiološki ishodi i kliničko liječenje procijenjeni su u novijoj studiji u kojoj je troponin I visoke osjetljivosti izmjeren kod 1.038 pacijenata sa sumnjom na AKS.[11] Vrijed-

Incidence and mode of presentation

Temporal trends for the global coronary epidemic vary by region but in most developed countries mortality is in decline.[1] Lifestyle adjustments have contributed to this decline — most recently, the implementation of comprehensive smoke-free legislation in many countries that has already caused significant reductions in acute coronary events.[2] Smoking, a potent thrombogenic stimulus, is a major determinant of ST elevation myocardial infarction (STEMI)[3] and a recent analysis from Kaiser Permanente in California — where smoke-free legislation is strictly enforced — showed a 62% decline in STEMI between 1999 and 2008 while non-ST segment elevation myocardial infarction (NSTEMI) increased by 30%.[4] Overall, there was a 24% reduction in hospitalisations for acute coronary syndromes (ACS) despite lowering of diagnostic thresholds by sensitive troponin biomarkers.[5] This was accompanied by improvement in the age- and sex- adjusted 30-day mortality from 10.5% in 1999 to 7.8% in 2008. Increasing rates of interventional management no doubt contributed to the improved outcomes but parallel increases in plaque-stabilising treatment with high-dose statins must also have played a role[6] because vulnerable thin-cap fibroatheromas, often remote from the infarct-related artery and unrelated to stenosis severity, are the sites at which recurrent plaque events usually occur.[7,8]

Diagnosis

Diagnostic definitions of ACS are internationally agreed based on troponin release and symptomatic, electrocardiographic, or functional criteria.[9]

Troponins

Demonstration of a changing troponin concentration in the first 24 h with at least one value above the decision limit is central to the diagnosis of acute myocardial infarction (AMI). Now available are high-sensitivity troponin assays permitting significant reductions in the threshold for detection. An early study evaluated four high-sensitivity assays in 718 patients with suspected ACS, 17% of whom had AMI. Diagnostic performance was excellent, the area under the receiver operator curves ranging from 0.95 to 0.96 compared with 0.90 for the standard assay.[10] The implications for cardiac outcomes and clinical management were assessed in a more recent study in which high-sensitivity troponin I was measured in 1038 patients with suspected ACS.[11] Values below the previous limit of detection

nosti ispod prethodne granice detekcije (0,20 ng/ml) — konvencionalno smatrane "normalnima" — pokazale su povezanost sa smrtnim ishodom i ne-fatalnim IM, uz stope od 7% i 39% za vrijednosti troponina <0,05 ng/ml, odnosno 0,05-0,19 ng/ml. Kad su istraživači spustili dijagnostički prag na 0,05 ng/ml kod daljnjih 1.054 pacijenata, komunicirajući s liječnicima, rizik od smrti i ponovljenog infarkta miokarda kod pacijenata s vrijednostima troponina 0,05-0,19 ng/ml je smanjen sa 39% na 12%. Istraživači su zaključili da snižavanje dijagnostičkog praga kliničkom primjenom visoko-osjetljivih troponinskih testova ima potencijal identificiranja mnogih visokorizičnih pojedinaca sa sumnjom na AKS te dovodi do značajnog poboljšanja prognoze.

Drugi dijagnostički biomarkeri

Studije koje procjenjuju nove biomarkere za ranu dijagnozu IM su bile predmet nedavne sistematske ocjene.[12] Kvaliteta ovih studija je često bila slaba te je svega 16% dalo informacije o dodatnoj vrijednosti u usporedbi s ostalim dijagnostičkim podacima. Primjerice, čini se da je mioglobin koristan za isključivanje IM u prvih 6 sati, no dokazi da donosi dodatnu vrijednost kliničkim simptomima, EKG i testiranju troponina su ograničeni. Od novih dijagnostičkih biomarkera, ishemijom modificirani albumin i srčanog proteina koji veže masne kiseline (H-FABP) su se na početku pokazali obećavajući, no meta-analiza je već zaključila da H-FABP ne ispunjava zahtjeve potrebne za ranu dijagnozu kada se koristi kao samostalan test te traži dokaze o dodatnoj vrijednosti kliničkoj procjeni drugih dijagnostičkih testova.[13]

Brza dijagnoza uz pacijenta primjenom panela biomarkera

Dvije nedavne studije su procijenile imaju li paneli biomarkera specifičnu ulogu u ranoj dijagnozi IM u hitnoj službi, a obje su koristile brze testove za troponin I, kreatin kinazu-MB (CK-MB) i mioglobin. RATPAC je okupio 2.243 pacijenata sa sumnjom na IM i randomizirao ih na standardnu obradu ili procjenu panelima po zaprimanju u hitnu službu te 90 minuta nakon toga.[14] Procjena pomoću brzih testova povezana je sa 32% "uspješnih" (bez povratka s težim koronarnim epizodama) otpusta iz hitne službe, u usporedbi s 13% za standardnu obradu; nije bilo utjecaja na korištenje bolničkih kreveta. Međutim, podstudija za proučavanje dijagnostičke učinkovitosti pojedinačni kardioloških biomarkera i njihove točnosti za konačnu dijagnozu AIM je pokazala da brzi testovi za mioglobin i CK-MB ne pružaju dodatne dijagnostičke informacije u usporedbi s troponinom I u ranoj dijagnozi ili isključivanje IM.[15] ASPECT je bila opservacijska studija s uključenih 3.582 pacijenta kod kojih je alat za procjentu nazvan ADP, koji se sastojao od bodovanja po TIMI ljestvici zajedno s panelom brzih dijagnostičkih testova i EKG zapisom, identificirao 352 pacijenta kao niskorizična.[16] Samo tri pacijenta su doživjela težu kardiovaskularnu epizodu, što ADP čini visoko osjetljivim alatom za isključivanje mogućnosti IM kod niskorizičnih pacijenata, što odražava negativna prediktivna vrijednost od 99,1%. Međutim, u studiji ASPECT nije bilo kontrolne skupine, niti je bilo analize dodatne vri-

(0.20 ng/ml) — conventionally considered 'normal' — showed graded association with death or non-fatal myocardial infarction (MI), with rates of 7% and 39% for troponin concentrations of <0.05 ng/ml and 0.05-0.19 ng/ml, respectively. When the investigators lowered the diagnostic threshold to 0.05 ng/ml in a further 1054 patients, communicating troponin values to clinicians, the risk of death and recurrent MI in patients with troponin concentrations 0.05-0.19 ng/ml was reduced from 39% to 12%. The investigators concluded that lowering the diagnostic threshold by clinical application of high-sensitivity troponin assay has the potential to identify many high-risk individuals with suspected ACS and produce major improvements in their prognosis.

Other diagnostic biomarkers

Studies evaluating new biomarkers for the early diagnosis of MI have been the subject of a recent systematic review.[12] The quality of these studies has often been poor with only 16% providing any information about incremental value compared with other diagnostic data. Myoglobin, for example, appears to be useful to rule out MI in the first 6 h but evidence that it adds value to clinical symptoms, ECG and troponin testing is limited. Of the new diagnostic biomarkers, ischaemia-modified albumin and heart-type fatty acid-binding protein (H-FABP) showed initial promise, but already a meta-analysis has concluded that H-FABP does not fulfil the requirements needed for early diagnosis when used as a stand-alone test and called for evidence that it adds to clinical evaluation and other diagnostic tests.[13]

Point-of-care diagnosis with a panel of biomarkers

Whether biomarker panels have a specific role for early diagnosis of MI in the emergency room has been evaluated in two recent studies, both using a point-of-care panel of troponin I, creatine kinase-MB (CK-MB) and myoglobin. RATPAC recruited 2243 patients with suspected MI and randomised them to standard care or panel evaluation on admission to the emergency room and 90 min later.[14] Point-of-care panel evaluation was associated with a 32% rate of 'successful' (no re-attendance with major coronary events) discharge from the emergency room, compared with 13% for standard care; hospital bed use was unaffected. However, a substudy to examine the diagnostic efficiency of the individual cardiac markers and their accuracy for the final diagnosis of AMI showed that point-of-care myoglobin and CK-MB did not provide further diagnostic information over that provided by troponin I for early diagnosis or exclusion of MI.[15] ASPECT was an observational study of 3582 patients in which an accelerated diagnostic panel (ADP) of TIMI score, coupled with the point-of-care panel of biomarkers and ECG findings, identified 352 as low risk.[16] Only three of these patients went on to experience a major adverse cardiac event, making the ADP a highly sensitive rule-out for MI in low-risk patients, as reflected by a negative predictive value of 99.1%. However, there was no control group in ASPECT, nor an analysis of the incremental value offered by individual components of

jednosti kroz individualne komponente panela biomarkera. Stoga se, na temelju RATPAC analize podskupina, jasno čini da troponin ostaje najkorisniji biomarker za dijagnozu IM u hitnoj službi i trenutni dokazi su nedovoljni da bi podržali primjenu panela biomarkera.

Elektrokardiogram

Smjernice preporučaju hitnu reperfuzijsku terapiju prema protokolu za STEMI kod pacijenata sa sumnjom na IM i blokom lijeve grane (LBBB). Međutim, retrospektivna analiza 892 pacijenata u Registru STEMI s Mayo klinike, je pokazala da je od 36 pacijenata s novim LBBB, svega njih 12 (33%) kao konačnu dijagnozu imalo AIM.[17] Ovi podaci pokazuju da je LBBB ograničeno dijagnostičko sredstvo kod sumnje na IM te pruža temelj za novu dijagnostičku strategiju kod ove visokorizične skupine. Također, visokorizični su i pacijenti s AIM uzrokovanim okluzijom lijeve prednje silazne koronarne arterije (LAD). Izvješće kako bi ovo moglo biti povezano s prepoznatljivim EKG nalazom je sada potvrđeno kod serije od 35 pacijenata koji su podvrgnuti primarnom PCI LAD, od kojih su svi pokazali depresiju ST-segmenta na J-točki uz uzlazne ST-segmente i visoke, simetrične T-valove u prekordijalnim odvodima 12-kanalnog EKG.[18,19] Autori preporučaju da bi ovaj EKG nalaz kod pacijenata kod kojih se sumnja na IM trebao potaknuti trijažu na neposrednu reperfuzijsku terapiju.

Slikovni prikaz

Ehogardiografija daje najpristupačniji slikovni prikaz kod dijagnoze AIM, identificirajući novonastale abnormalnosti regionalnog gibanja zida lijeve klijetke. Nedavno je opisana nova dijagnostička primjena kod identificiranja pacijenata s NSTEMI koji imaju potpunu koronarnu okluziju.[20] Kod takvih pacijenata, cirkumferencijalno naprezanje mjereno unutar 1 sat od prijma je od neovisnog dijagnostičkog značaja, a vrijednosti ≥10% pokazuju 90% osjetljivost i 88% osjetljivost na angiografsku koronarnu okluziju. Autori predlažu da bi se mjerenje naprezanja u akutnoj fazi NSTEMI moglo koristiti u trijaži pacijenata za neposrednu reperfuzijsku terapiju.

Stratifikacija rizika

Rizik od smrti i drugih ishemijskih događaja kod pacijenata s AKS znatno varira prema dijagnostičkim fenotipovima. Objektivni kriteriji za kvantifikaciju rizika sada se sve više koriste za usmjeravanje liječenja i određivanje prognoze.

Klinički čimbenici

U svakodnevnoj kliničkoj praksi liječnici intuitivno koriste kliničke čimbenike. Poznato je da se rizik povećava s godinama i da postoje značajne razlike vezanmo uz spol — primjerice mlade žene sa STEMI imaju 15-20% veći rizik smrtnog ishoda od muškaraca.[21] EKG kriteriji[22] i rutinski biokemijski nalazi također se koriste za stratifikaciju rizika, ishod bolestii se pogoršava s hiperglikemijom pri prijmu, a čini se također i s hipoglikemijom pri prijmu.[23,24] Iako se li-

the biomarker panel. Based on the RATPAC subgroup analysis, therefore, it seems clear that troponin remains the most useful biomarker for diagnosis of MI in the emergency room and current evidence is insufficient to advocate biomarker panels for this purpose.

Electrocardiogram

Guideline recommendations are for urgent reperfusion therapy according to STEMI pathways in patients with suspected MI presenting with left bundle branch block (LBBB). However, a retrospective analysis of 892 patients in a Mayo Clinic STEMI registry, found that of the 36 who presented with new LBBB, only 12 (33%) had a final diagnosis of AMI.[17] These data show that LBBB is of limited diagnostic utility in suspected MI and provide a case for new diagnostic strategies in this high-risk group. Also at high risk are patients with AMI caused by proximal left anterior descending coronary artery (LAD) occlusion. A report that this may be associated with a distinct ECG pattern has now been confirmed in a series of 35 patients who underwent primary percutaneous coronary intervention (PCI) of the LAD, all of whom showed ST-segment depression at the J-point with up-sloping ST segments and tall, symmetrical T-waves in the precordial leads of the 12-lead ECG.[18,19] The authors recommend that this ECG pattern in patients presenting with suspected MI should prompt triage for immediate reperfusion therapy.

Imaging

Echocardiography provides the most readily available imaging modality for acute phase diagnosis of MI by identifying new left ventricular regional wall motion abnormality. A new diagnostic application for identifying those patients with NSTEMI who have complete coronary occlusions was recently described.[20] In such patients, circumferential strain measured within 1 h of admission was independently diagnostic, values ≥10% showing 90% sensitivity and 88% sensitivity for angiographic coronary occlusion. The authors suggest that strain measurements in the acute phase of NSTEMI might be used for triaging patients for immediate reperfusion therapy.

Risk stratification

The risk of death and other ischaemic events in patients with ACS varies considerably across diagnostic phenotypes. Objective criteria to quantify risk are now increasingly used to guide treatment and determine prognosis.

Clinical factors

Clinical factors are used intuitively by clinicians. They recognise that risk increases with age and shows important gender differences-young women with STEMI, for example, having a 15-20% higher mortality risk than men.[21] ECG criteria[22] and routine biochemistry are also used for risk stratification, outcomes worsening with admission hyperglycaemia and also it seems with admission hypoglycaemia.[23,24] Despite clinicians' reliance on clinical assessments

ječnici pouzdaju u kliničku procjenu rizika jasno je da su često greške moguće, a nedavna studija je pokazala slabu povezanost s objektivnim mjerama rizika koje koriste provjerene ljestvice rizika.[25]

Dijagnostički biomarkeri

Povećano otpuštanje troponina kod NSTEMI povezuje se s proporcionalnim povećanjem rizika od smrtonosnih aritmija, kardiogenog šoka, novonastalog zatajivanja srca i smrti.[26] C-reaktivni protein, najviše proučavani prognostički biomarker, također umjereno predviđa neželjene ishode kod AKS, a nedavna meta-analiza izvještava prosječni RR od 2,18 (1,77 do 2,68) za gornju (>10 mg/l) u usporedbi s donjom (≥3 mg/l) kategorijom vrijednosti.[27] Međutim, pojedinačni biomarkeri tek moraju pronaći korisnu kliničku ulogu — nedavno 5-godišnje praćenje pacijenata s NSTEMI uključenima u studiju FRISC II izvještava da N-terminalni pro-moždani natriuretski peptid (NT-proBNP), C-reaktivni protein, troponin I i procijenjena glomerularna stopa filtracije ne donose dodatnu prognostičku vrijednost za utvrđivanje indikatora rizika, izuzev NT-proBNP-a za 6-tjedne ishode.[28] Kombiniranje višestrukih biomarkera može poboljšati prognostičku vrijednost kod neželjenih ishoda, no i dalje se čeka potvrda dodatne vrijednosti u usporedbi poznatim ljestvicama rizika.[29]

Ljestvice rizika

Potvrđene ljestvice rizika koje se temelje na nizu odmah dostupnih čimbenika pružaju najučinkovitiji način stratifikacije rizika kod pacijenata s AKS. GRACE ljestvica u širokoj je primjeni, a u komparativnoj validacijskoj studiji koja je uključivala 100.686 ispitanika s AKS rezultat kod predviđanja mortaliteta je bio dobar uspoređujući s ostalim alatima za procjenu rizika, ulključujući PURSUIT, GUSTO-1, GRACE. SRI i EMMACE.[30] Čini se da GRACE ljestvica nije izgubila ništa od svoje kliničke vrijednosti s pojavom visoko osjetljivih troponina. U međunarodnoj studiji 370 pacijenata s AKS, površina ispod krivulje GRACE ljestvice iznosila je 0,87 i 0,88 za bolnički i 1-godišnji mortalitet, a dodatak rezultata visoko-osjetljivih troponina nije donio poboljšanje u predviđanju mortaliteta.[31]

Primarna perkutana koronarna intervencija

Javno izvješće MINAP za Englesku i Wales bilježi da je 70% pacijenata sa STEMI liječeno reperfuzijskom terapijom tijekom 2010./2011. godine, od čega je 81% liječeno primarnim PCI.[32] Pomak prema primarnoj PCI, temeljem dokaza kontinuirane koristi za smanjenje smrtnosti u usporedbi s fibrinolizom,[33] je poduprijet uspostavom regionalnih mreža koje su definirale lokalne standarde skrbi i osigurale infrastrukturu za popunjavanje osoblja kardioloških centara.[34,35]

Pravodobno liječenje je nužno kako bi se maksimizirala prognostička korist,[36,37] te koliko god je važno ostvariti "door-to-ballon" vrijeme unutar 90 minuta, također je potrebno u obzir uzeti i ostala kašnjenja u procesu zdravstvene skrbi. Stoga je analiza danskog registra 6.209 pacijenata sa STEMI ustanovila da su "kašnjenje sustava" (vri-

of risk it is now clear that they often get it wrong and a recent study has shown little association with objective measures of risk using validated risk scores.[25]

Diagnostic biomarkers

Increasing troponin release in NSTEMI is associated with a proportionate increase in the risk of lethal arrhythmias, cardiogenic shock, new heart failure and death.[26] C-reactive protein, the most widely studied prognostic biomarker, is also moderately predictive of adverse outcomes in ACS, a recent meta-analysis reporting a pooled RR of 2.18 (1.77 to 2.68) for the top (>10 mg/l) compared with the bottom (?3 mg/l) category of values.[27] Generally speaking, however, individual biomarkers have yet to find a useful clinical role — a recent 5-year follow-up of patients with NSTEMI included in FRISC II reporting that none of N-terminal pro-brain natriuretic peptide (NT-proBNP), C-reactive protein, cardiac troponin I and estimated glomerular filtration rate provided incremental prognostic value to established risk indicators, except NT-proBNP for 6-week outcomes.[28] Combining multiple biomarkers may improve predictive power for adverse outcomes but confirmation of incremental value over established risk scores is still awaited.[29]

Risk scores

Validated risk scores based on a range of readily available factors provide the most effective means of risk stratifying patients with acute coronary syndromes. The GRACE score is widely used and in a comparative validation study involving 100,686 cases of ACS its discriminative performance in predicting mortality compared favourably with a range of other risk models including PURSUIT, GUSTO-1, GRACE, SRI and EMMACE.[30] The GRACE score appears to have lost none of its clinical value with the availability of high-sensitivity cardiac troponin assays. In an international cohort of 370 patients with ACS, the area under the curve of the GRACE score was 0.87 and 0.88 for in-hospital and 1-year mortality, and addition of high-sensitivity cardiac troponin produced no improvement in the mortality prediction.[31]

Primary percutaneous coronary intervention

The MINAP public report for England and Wales records that 70% of all patients with STEMI received reperfusion therapy in 2010/2011, of whom 81% received primary PCI.[32] The drive towards primary PCI, based on evidence of a sustained mortality benefit compared with fibrinolysis,[33] has been underpinned by the establishment of regional networks that have defined local standards of care and provided infrastructure for staffing heart attack centres.[34,35]

Timely treatment is essential to maximise prognostic benefit,[36,37] and important as it is to achieve door-to-balloon times within 90 min, other intrinsic delays within the healthcare process also need consideration. Thus, a Danish registry analysis of 6,209 patients with STEMI found that 'system delay' (time from first contact with the health-

jeme od prvog kontakta sa zdravstvenim sustavom do početka reperfuzijske terapije) i "door-to-ballon" vrijeme bili ključni promjenjivi čimbenik rizika, uz omjer rizika za mortalitet tijekom sljedećih 3,4 godine od 1,22 (95% CI 1,15 do 1,29; p<0,001) po 1 satu porasta kašnjenja sustava.[38] Rezultati naglašavaju važnost kratkoće vremena transfera iz bolnica bez mogućnosti PCI i postavljanja prehospitalne dijagnoze kako bi se osigurao izravan prijevoz pacijenata sa STEMI u intervencijske centre. Također su važne i strategije za smanjenje vremena potrebnog osobama s bolovima u prsištu do poziva hitnoj službi. Unatoč kampanji u SAD koja je imala za cilj povećanje svijesti žena o njihovom riziku od srčanih bolesti, nedavna studija je ustanovila da to nije imalo utjecaja na razliku u smrtnosti između spolova ili vrijeme potrebnodo poziva hitnoj službi koje je kod žena značajnije duže nego kod muškaraca.[39]

Vaskularni pristup

Primarna PCI radijalnim umjesto femoralnog pristupa predstavlja preferirani pristup kod sve većeg broja intervencijskih kardiologa.[40] Čini se da je njezina glavna prednost smanjena učestalost komplikacija krvarenja. Randomizirana studija RIVAL koja je proučavala radijalni nasuprot femoralnom pristupu kod 7.021 pacijenata s AKS je izvijestila o trendu prema nižoj učestalosti krvarenja nakon 30 dana (0,7% naspram 0,9%), povezanima sa znatno nižim stopama komplikacija mjesta pristupa, uključujući velike hematome i pseudoaneurizme.[41] Nalazi su bili slični u nedavnoj opservacijskoj studiji kod 1.051 ispitanika s primarnom PCI i učestalosti vaskularnih komplikacija od 0% i 1,9% za radijalni naspram femoralnog pristupa.[42] Međutim, studija RIVAL nije ustanovila dobrobiti radijalnog pristupa na ishode, a femoralni pristup i dalje preferiraju mnogi kardiolozi[43] jer je predvidljiviji, a vrijeme intervencije može biti kraće nego kod radijalnog pristupa.[44,45]

Implantacija stenta

Zabrinutost zbog tromboze stenta rezultirala je preporukama za metalne stentove (BMS) kod primarne PCI, no randomizirane studije su potvrdile prednosti stentova koji otpuštaju lijekove (DES). Trogodišnji rezultati studije HORIZONS-AMI su izvjestili o nižoj učestalosti revaskularizacije ciljnih lezija kod 2257 pacijenata randomiziranih na DES s paklitakselom nego kod 749 pacijenata randomiziranih na BMS (9,4% naspram 15,1%).[46] Nije bilo značajne razlike ovisne o tipu stenta za učestalost smrtnog ishoda, ponovnog infarkta, moždanog udara ili tromboze stenta. Stoga DES imaju prednost kod primarne PCI, no to zahtjeva od pacijenta punih 12 mjeseci dvostrukog antitrombocitnog liječenja. Ako se planira hitan kirurški zahvat ili iz nekih drugih razloga postoji visoki rizik od krvarenja trebalo bi odabrati BMS.

Intervencija vodeće lezije ili više žila

Glavna svrha primarne PCI je ostvariti reperfuziju ugroženog miokarda otvaranjem vodeće lezije koronarne arterije. Da li je sigurno ili poželjno tretirati bolest unutar lezije koja nije vodeća već tijekom postupka primarne PCI ili pak kao naknadni postupak predstavlja predmet nedavne

care system to the initiation of reperfusion therapy) — as well as door-to-balloon time — was a key modifiable risk factor, with an HR for mortality during the next 3.4 years of 1.22 (95% CI 1.15 to 1.29; p<0.001) per 1 h increase in system delay.[38] The findings emphasise the importance of minimising transfer times from non-PCI hospitals and introducing policies of prehospital diagnosis to permit direct delivery of patients with STEMI to interventional centres. Also important are strategies to reduce the time it takes people with chest pain to call the emergency services. Women take significantly longer than men but, despite a US campaign to increase women's awareness of their risk of heart disease, a recent study found it had no effect on the gender gap or the time it took women to call the emergency services.[39]

Vascular access

Primary PCI by radial rather than femoral access is the preferred approach for an increasing number of operators.[40] Its main advantage appears to be a lower rate of bleeding complications — the randomised RIVAL trial of radial versus femoral access in 7,021 patients with ACS reporting 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.[41] Findings were similar in a recent observational study of 1,051 primary PCI cases with vascular complication rates of 0% and 1.9% for radial versus femoral access.[42] However, RIVAL found no outcome advantage for radial access, and femoral access is still preferred by many operators[43] because access is more predictable and procedure times may be shorter than with the radial approach.[44,45]

Stenting

Concerns about stent thrombosis led to recommendations for bare metal stents in primary PCI but randomised trials have now confirmed important advantages for drug-eluting stents. The HORIZONS-AMI 3-year results showed lower rates of target lesion revascularisation for the 2,257 patients randomised to paclitaxel-eluting stents than for the 749 patients randomised to bare metal stents (9.4% vs 15.1%).[46] There was no difference by stent type in rates of death, reinfarction, stroke or stent thrombosis. Drug-eluting stents are, therefore, preferred in primary PCI but they commit the patient to a full 12 months of dual antiplatelet treatment and if urgent surgery is planned or there is a high risk of bleeding for other reasons bare metal stents should be chosen.

Culprit lesion versus multivessel PCI

The main purpose of primary PCI is to achieve reperfusion of jeopardised myocardium by reopening the culprit coronary artery. Whether it is safe or desirable to treat disease within non-culprit vessels during the primary PCI procedure or as a staged procedure afterwards has been the subject of recent investigation. A small randomised trial of 214 patients with multivessel disease found that adverse event rates during a mean follow-up of 2.5 years

studije. Mala randomizirana studija s uključenih 214 pacijenata s višežilnom bolesti je ustanovila da je učestalost neželjenih ishoda tijekom srednjeg trajanja praćenja od 2,5 godine bila viša kod intervencije na vodećoj leziji nego kod zahvata na više žila bilo da su obavljeni tijekom postupka primarne PCI ili, još bolje, kao naknadno planirani postupak.[47] Ova studija je sada uključena u meta-analizu četiri prospektivne i 14 retrospektivnih studija koje uključuju 40.280 pacijenata, koje su došle do sličnog zaključka koji pokazuje da je planirani PCI povezan s nižim mortalitetom u usporedbi s intervencijom vodeće lezije.[48] Međutim, višežilna intervencija tijekom primarne PCI povezan je s najvišim mortalitetom. Post hoc analiza studije HORIZONS-AMI je također ustvrdila da je planirani PCI povezan s nižim 1-godišnjim mortalitetom u usporedbi s PCI vodeće lezije (2,3% nasuprot 9,2%).[49] Ovi podaci dosljedno pokazuju da se višežilna bolest najbolje rješava elektivno kao planirani postupak nakon što se obavi primarna PCI.

Trombektomija

Trombotska koronarna okluzija je patološki događaj koji potiče STEMI i daje razlog za dodatnu trombektomiju tijekom primarne PCI. Razvijen je čitav niz uređaja za ovu svrhu no najjednostavniji, manualna aspiracija tromba, se pokazao najboljim, s dokazima bolje reperfuzije tijekom akutne faze STEMI što daje prednost kod preživljavanja nakon 1 godine usporednu s uobičajenom primarnom PCI.[50,51] Oslikavanje magnetnom rezonancijom je potvrdilo da aspiracija tromba smanjuje mikrovaskularnu opstrukciju tijekom primarne PCI i ograničava veličinu infarkta nakon 3 mjeseca.[52] Novija analiza individualnih podataka o pacijentima iz tri randomizirane studije je ustanovila da je trend pogoršanja reperfuzije miokarda s prolaskom vremena od prijma do primarne PCI učinkovito izjednačen aspiracijom tromba, što sugerira specifičnu dobrobit u slučaju kašnjenja s postupkom.[53] Složeniji uređaji za trombektomiju nisu preporučenu za uporabu kod pacijenata sa STEMI. Procjena veličine infarkta u dvije studije — JETSTENT (usporedba Agiojet reolitičke trombektomije s primarnim izravnim stentingom) i PREPARE (usporedba simultane proksimalne embolijske zaštite i manualne aspiracije tromba s manualnom aspiracijom tromba) nije pokazala značajnu korist od ovih strategija.[54,55] S ovim su dosljedne i meta-analize studija trombeoktomije koje su pokazale da je korist za smanjenje smrtnosti kod pacijenata randomiziranih na ekstrakciju tromba ograničena na pacijente liječene manualnom trombektomijom.[56]

Antitrombocitne strategije liječenja

Trenutne preporuke ukazuju na početnu (udarnu) dozu acetilsalicilne kiseline (ASK) i klopidogrela neposredno prije primarne PCI, a potom slijedi doza održavanja. Dodatno liječenje inhibitorima IIb/IIIa receptora pruža intenzivniju inhibiciju trombocita u akutnoj fazi. Glavna svrha liječenja je povećanje otapanja tromba i sprječavanje ponavljanja trombotskih događaja, naročito tromboze stenta unutar 9-12 mjeseci koliko je potrebno DES da bi endotelizirali (1-3 mjeseca za BMS). Sada su dostupni noviji lijekovi koji snažnije od klopidogrela blokiraju ADP P2Y12 receptor[57] te su istraživani u kombinaciji s ASK kod pacije-

were higher with culprit PCI than with multivessel PCI whether performed during the primary PCI procedure or, better, as a staged procedure afterwards.[47] This trial has now been included in a meta-analysis of four prospective and 14 retrospective studies involving 40,280 patients, which came to a similar conclusion in showing that staged PCI was associated with lower mortality compared with culprit PCI.[48] However, multivessel PCI during the primary procedure was associated with the highest mortality. A post hoc analysis of the HORIZONS-AMI trial also found that staged PCI was associated with lower 1-year mortality compared with culprit PCI (2.3% vs 9.2%).[49] These data, are consistent in showing that multivessel disease is best dealt with electively as a staged procedure after the primary PCI procedure has been completed.

Thrombectomy

Thrombotic coronary occlusion is the pathological event triggering STEMI and provides the logic for adjunctive thrombectomy during primary PCI. A variety of devices have been developed for this purpose but the simplest, manual thrombus aspiration, has emerged as the best, with evidence of better reperfusion during the acute phase of STEMI translating into a survival advantage at 1 year compared with conventional primary PCI.[50,51] MRI has confirmed that thrombus aspiration reduces microvascular obstruction during primary PCI and limits infarct size at 3 months.[52] A more recent analysis of pooled individual patient data from three randomised trials found that the trend for worsening myocardial reperfusion with time from admission to primary PCI was effectively abolished by thrombus aspiration, suggesting particular benefits in the event of procedural delay.[53] More complex thrombectomy devices are not recommended for use in STEMI. Thus assessments of infarct size reduction in two trials — JETSTENT comparing Angiojet rheolytic thrombectomy with primary direct stenting and PREPARE comparing simultaneous proximal embolic protection and manual thrombus aspiration with manual thrombus aspiration — showed no significant benefit of these device strategies.[54,55] Consistent with this is a meta-analysis of thrombectomy trials showing that the mortality benefit for patients randomised to thrombus extraction is confined to patients treated with manual thrombectomy.[56]

Antiplatelet strategies

Current recommendations are for loading doses of aspirin and clopidogrel immediately before primary PCI followed by maintenance treatment. Adjunctive treatment with GPIIb/IIIa receptor blockers provides more intensive platelet inhibition in the acute phase. The main purpose of treatment is to enhance thrombus resolution and to prevent recurrent thrombotic events, particularly stent thrombosis in the 9-12 months it takes for drug-eluting struts to endothelialise (1-3 months for bare metal struts). Newer, drugs that block the ADP P2Y12 receptor more potently than clopidogrel are now available[57] and have been evaluated in combination with aspirin in patients undergoing primary PCI. In the TRITON-TIMI 38 trial of dual antiplatelet treatment, prasugrel reduced the primary outcome of cardio-

nata podvrgnutih primarnoj PCI. U studiji dvostrukog antitrombocitnog liječenja TRITON-TIMI 38 prasugrel je reducirao primarni zajednički ishod (kardiovaskularna smrt, nefatalni IM i nefatalni moždani udar) u usporedbi s klopidogrelom (6,5% naspram 9,5%), ali je to bilo povezano sa značajno većim rizikom od velikog krvarenja, uključujući i krvarenje sa smrtnim ishodom, što postavlja upite o sigurnosti lijeka.[58] Tikagrelor je također procijenjen u usporedbi s klopidogrelom u podstudiji studije PLATO te se, kao i prasugrel, dokazao učinkovitijim u smanjenju primarnog zajedničkog ishoda (kardiovaskularna smrt, IM ili moždanog udara) iako je apsolutna razlika bila mala (9,0% naspram 10,7%).[59] Međutim, interesantno je da se pojavilo povećana učestalost krvarenja te tikagrelor sada ima preporuku za uporabu kod primarne PCI, iako njegovo konačno mjesto u terapeutskom arsenalu mora pričekati studije isplativosti i dugoročne sigurnosti.

Abciksimab, primjenjen intravenozno, predstavlja najšire korišten inhibitor IIb/IIIa receptora kod pacijenata sa STEMI koji su podvrgnuti primarnoj PCI. Koristi se čine obrnuto povezane s procesom upale[60], a mogle bi se povećati intrakoronarnom primjenom, što je potvrdila meta-analiza koja kod ovakve primjene izvještava o poboljšanim kliničkim ishodima.[61] Međutim, abciksimab je skup i sada postoje studije koje potvrđuju neinferiornost malih molekula inhibitora IIb/IIIa receptora. Stoga su istraživači analizirajući podatke Švedskog registara koronarografije i angioplastike usporedili rezultate 2.355 pacijenata s primarnom PCI koji su liječeni eptifibatidom s drugih 9.124 koji su liječeni abciksimabom te su pronašli sličnu učestalost smrtnosti od IM tijekom jednogodišnjeg praćenja (15,0% naspram 15,7%).[62] U sličnoj studiji, 427 pacijenata randomiziranih ili na eptifibatid ili abciksimab je pokazalo identičnu učestalost kompletne rezolucije ST-segmenta 60 minuta nakon primarne PCI (62,6% nasuprot 56,3%) te nije bilo registrirano značajnijih razlika između kardiovaskularnih ishoda.[63] U studiji On-TIME 2, još je jedan spoj malih molekula, tirofiban, u kombinaciji s ASK i klopidogrelom, rezultirao učinkovitijom inhibicijom trombocita od same ASK i klopidogrela kod pacijenata koji su bili podvrgnuti primarnoj PCI. Stupanj trombocitne inhibicije je pokazao značajan odnos s glavnim neželjenim kardiološkim epizodama, uključujući i trombozu stenta.[64] Ovi nalazi moraju tek penetrirati u međunarodne smjernice, no mnogi centri već sada prelaze s abciksimaba na spojeve malih molekula kako bi se smanjili farmakološki troškovi.

Ostali antitrombocitni lijekovi

Fondaparinuks

Intravenozni heparin tijekom primarne PCI dodatno poboljšava otapanje tromba tijekom intervencije, a fondaparinuks, sintetski inhibitor faktora Xa ima prednosti u odnosu na niskomolekularni heparin. Nedavna zajednička analiza 26.512 pacijenata iz studija OASIS 5 i 6 randomiziranih na 2,5 mg fondaparinuksa dnevno ili strategiju koja se temelji na heparinu riješile su nesigurnost vezanu za kliničku primjene fondaparinuksa u pacijenata koji se podvrgavaju liječenju primjenom PCI pokazujući bolji učinak na zajednički (smrt, IM, moždani udar ili veće krvarenje) ishode (10,8% naspram 9,4%; HR=0,87; p=0,008) u podskupini od 19.085 pacijenata koji su invazivno liječeni.[65]

vascular death, non-fatal MI and non-fatal stroke compared with clopidogrel (6.5% vs 9.5%), but this was associated with a significantly greater risk of major bleeding, including fatal bleeding, raising important safety concerns.[58] Ticagrelor has also been evaluated against clopidogrel in a substudy of the PLATO trial and like prasugrel it proved more effective in reducing the primary outcome of cardiovascular death, MI or stroke, although the absolute difference was small (9.0% vs 10.7%).[59] Strikingly, however, there appeared to be enhanced bleeding, and ticagrelor now has a guideline recommendation for use in primary PCI, although its final place in the therapeutic arsenal must await cost-effectiveness and long-term safety studies.

Abciximab, given intravenously, has been the most widely used GPIIb/IIIa receptor blocker in patients with STEMI undergoing primary PCI. Benefits appear to be inversely related to inflammatory burden[60] and may be enhanced by intracoronary administration, a recent meta-analysis reporting improved clinical outcomes by this route.[61] However, abciximab is expensive and there are now studies confirming non-inferiority of 'small-molecule' GPIIb/IIIa receptor blockers. Thus, investigators using the Swedish Coronary Angiography and Angioplasty Registry compared 2,355 primary PCI patients who received eptifibatide with 9,124 who received abciximab and found similar rates of death or MI during 1-year follow-up (15.0% vs 15.7%).62 In a smaller study, 427 patients randomised either to eptifibatide or abciximab showed comparable rates of complete ST-segment resolution 60 min after primary PCI (62.6% vs 56.3%) with no significant differences between cardiovascular outcomes.[63] In the On-TIME 2 trial, another small molecule compound, tirofiban, in combination with aspirin and clopidogrel, provided more effective platelet inhibition than aspirin and clopidogrel alone in patients undergoing primary PCI. The degree of platelet inhibition showed significant relationship with major adverse cardiac events, including stent thrombosis.64 These findings have yet to penetrate international guidelines but many centres are now switching from abciximab to small-molecule compounds to reduce pharmacological costs.

Other antithrombotic drugs

Fondaparinux

Intravenous heparin during primary PCI further enhances thrombus resolution during primary PCI but ongoing treatment with low molecular weight heparin has now given way to fondaparinux, a synthetic factor Xa inhibitor. A recent individual patient-level combined analysis of 26,512 patients from the OASIS 5 and 6 trials who were randomised to fondaparinux 2.5 mg daily or a heparin-based strategy has resolved uncertainty about the clinical value of fondaparinux in patients undergoing primary PCI by showing a better net clinical composite of death, MI, stroke, or major bleeding (10.8% vs 9.4%; HR=0.87; p=0.008) in the subset of 19,085 patients treated invasively.[65] A similar benefit was found in patients treated conservatively. Fondaparinux is now widely used in preference to heparin in ACS.

Slična korist je ustanovljena i kod pacijenata koji su liječeni konzervativno. Fondaparinuks stoga ima prednost kod AKS u odnosu na heparin.

Bivalirudin

Bivalirudin je izravan inhibitor trombina koji je u studiji HORIZONS-AMI pokazao superiornost u usporedbi s kombiniranim liječenjem heparinom s IIb/IIIa inhibitorima, što je uvelike bilo posljedica manje učestalosti velikih krvarenja (4,9% naspram 8,3%).[66] Smrtnost od svih uzroka nakon 30 dana je također bio niža u skupini s bivalirudinom, s prisutnom dobrobiti i nakon 3 godine (5,9% naspram 7,7%), što je osiguralo preporuku za bivalirudin u primarnoj PCI.[46] Međutim, trebalo bi napomenuti da je femoralni arterijski pristup korišten kod 94,1% ispitanika u studiji HORIZONS-AMI pa nije poznato da li se redukcija krvarenja uz pomoć bivalirudina može jednako primijeniti na centre gdje se preferira radijalni pristup.

Fibrinolitičko liječenje

Dokazi da je fibrinoliza manje učinkovita od primarne PCI u hitnom liječenju STEMI su sada ojačani dokazima o smanjenoj troškovnoj učinkovitosti[67], a sada se ipak značajna manjina pacijenata u Engleskoj i Walesu liječi na ovaj način.[32] Ovo može biti opravdano ako se fibrinoliza može osigurati 30 minuta nakon prezentacije kada primarni PCI nije odmah dostupan, jer bi odgoda liječenja drugom strategijom bila povezana sa znatnim povećanjem smrtnosti.[36] Ovo opravdava programe prehospitalne trombolize, naročito u ruralnim područjima gdje je vrijeme transfera produljeno, ali entuzijazam ove strategije bi sada mogao biti umanjen dokazima iz MINAP registra koji pokazuju višu učestalost reinfarkta u usporedbi s bolničkim trombolitičkim liječenjem pacijenata sa STEMI.[68] Razlika u učestalosti reinfarkta je bila značajna samo za tenekteplazu (9,6% naspram 6,4%) no ne i za retaplazu, a bila je izrazito značajna kad je vrijeme transfera prelazilo 30 minuta. Razlika se pripisuje primjeni dodatnog antitrombotskog liječenja u ove dvije strategije liječenja. Interesantno je da su komplikacije krvarenja bile uobičajenije u bolničkom okruženju gdje je dodatna antitrombotska terapija bila agresivnija, što je dosljedno novijim podacima RIKS-HIA registra koji pokazuju porast krvarenja kod pacijenata koji su liječeni fibrinolitičkom terapijom od 2001. do 2006. kako je antitrombotsko liječenje postojalo sve učinkovitije.[69] Dostupnost potentnih blokatora ADP P2Y12 receptora je dovela do daljnje zabrinutosti o komplikacijama krvarenja te je stoga bilo utješno kad je dodatna analiza studije PLATO potvrdila da bi se bez povećanja rizika krvarenja učestalost događaja mogla smanjiti tikagrelorom u usporedbi s klopidogrelom.[70,71]

Uloga invazivnog liječenja nakon fibrinolitičkog liječenja kod bolesnika sa STEMI je pojašnjena u dvije nedavne meta-analize malih i srednjih velikih istraživanja koja su uspoređivala strategije rutinske rane koronarografije kod svih pacijenata u odnosu na odgođenu ili ishemijom vođenu koronarografiju.[72,73] Obje meta-analize su izvijestile da je rutinska rana koronarografija povezana sa smanjenom učestalosti ponovljenog infarkta miokarda i smrti te se ova strategija sada preporuča u međunarodnim smjernicama.

Bivalirudin

Bivalirudin is a direct thrombin inhibitor that showed superiority to a combined regimen of heparin plus a GPI-Ib/IIIa inhibitor in HORIZONS-AMI, largely owing to a lower rate of major bleeding (4.9% vs 8.3%).[66] All-cause mortality at 30 days was also lower in the bivalirudin group, with persistent benefit after 3 years (5.9% vs 7.7%), assuring a guideline recommendation for bivalirudin in primary PCI.46 It should be noted, however, that femoral artery access was used in 94.1% of the HORIZONS-AMI population and whether the reduction in bleeding with bivalirudin applies equally to centres where radial access is the preferred approach is not known.

Fibrinolytic treatment

Evidence that fibrinolysis is less effective than primary PCI in the emergency management of STEMI, has now been reinforced by evidence of reduced cost-effectiveness,[67] yet a significant minority of patients in England and Wales continue to be treated with it.[32] This may be justified if fibrinolysis can be delivered within 30 min after presentation when primary PCI is not immediately available, because treatment delays by either modality are associated with substantial increases in mortality.[36] This has provided justification for programmes of pre-hospital thrombolysis, particularly in rural regions where transport times are prolonged, but enthusiasm for this approach may now be diminished by evidence from the MINAP registry showing higher rates of reinfarction compared with in-hospital thrombolytic treatment for patients with STEMI.[68] The difference in reinfarction rates was only significant for tenecteplase (9.6% vs 6.4%), not reteplase, and was particularly marked when transport times exceeded 30 min. It was attributed to differences in the use of adjunctive antithrombotic treatment in the two treatment environments. Interestingly, bleeding complications were more common in the hospital environment where adjunctive antithrombotic treatment was more aggressive, consistent with recent data from RIKS-HIA showing that major bleeding complications among patients receiving fibrinolytic treatment continued to increase from 2001 to 2006 as antithrombotic treatments became more effective.[69] The availability of potent ADP P2Y12 receptor blockers has raised further concerns about bleeding complications, and it was gratifying, therefore, that the PLATO trial substudy confirmed that event rates could be reduced with ticagrelor compared with clopidogrel without an increase in bleeding risk.[70,71]

The role of invasive treatment after fibrinolytic treatment in STEMI has been clarified in two recent meta-analyses of small and medium-size trials comparing strategies of routine early angiography for all patients with deferred or ischaemia-guided angiography.[72,73] Both meta-analyses reported that routine early angiography was associated with reductions in the rates of recurrent MI and death and this strategy is now recommended in international guidelines.

Infarkt miokarda bez elevacije ST segmenta

NSTEMI je postao dominantan način prezentacije za pacijente s AIM, a u nedavnoj analizi iz Kaiser Permenente bio je zastupljen u 66,9% svih slučajeva.[4] Postoji percepcija da je NSTEMI relativno benigne progrnoze unatoč dokazima da je nakon 2 mjeseca prognoza lošija nego kod STEMI.[21,74] Ovo bi moglo objasniti tendenciju liječnika da suboptimalno liječe NSTEMI na osnovu nepodudaranja između percepcije i stvarnog rizika što iskrivljuje odluku o liječenju, te potiče paradoks rizika liječenja.[25] Stoga, unatoč lošijoj prognozi, manja je vjerojatnost da će pacijenti s NSTEMI dobiti optimalno liječenje u sekundarnoj prevenciji u usporedbi sa STEMI.[75] Nadalje, u studiji s uključenih 13.489 pacijenata zaprimljenih s NSTEMI iz registra MINAP, invazivno liječenje je povezano s boljim ishodima, no primijenjeno je neadekvatno, s nižom učestalosti u visokorizičnim skupinama, uključujući starije pacijente, žene, kao i one sa srčanim komorbiditetom.[76]

Hitno zbrinjavanje

Dvostruko antitrombocitno liječenje sa ASK i klopidogrelom je ključno u liječenju NSTEMI.[77] Uloga novih potentnijih blokatora ADP P2Y12 receptora ostaje neodređena, iako se tikagrelor čini obećavajući, temeljem učinkovitosti — smanjenja ishemijskih događaja u usporedbi s klopidogrelom kod NSTEMI, kao i STEMI, bez povećanja rizika od krvarenja.[78] Istodobno liječenje s fondaparinuksom ima prednost pred liječenjem primjenom enoksaparina temeljem rezultata studije OASIS 5 koja je usporedila ove lijekove kod 20 078 pacijenata s AKS.[79] Pacijenti randomizirani na fondaparinuks su pokazali 50% smanjenje većih krvarenja u usporedbi s enoksaparinom te nije bilo razlike u učestalosti ishemijskih događaja. Smanjenje rizika krvarenja je bila usporedivo bilo da su dodatno propisani klopidogrel ili inhibitori IIb/IIIa receptora[80], a troškovna učinkovitost je sada potvrđena.[81] Indikacije za bivalirudin kod NSTEMI je bilo teže definirati te iako ima dozvolu za uporabu u kombinaciji sa ASK i klopidogrelom, to je temeljeno na njegovom sigurnosnom profilu (niži rizik od krvarenja), dok njegova učinkovitost u smanjenju ishemijskih događaja nije veća od one kod heparina zajedno s inhibitorom IIb/IIIa ili pak bivalirudinom zajedno s inhibitorom IIb/IIIa receptora.[82]

Većina pacijenata s NSTEMI ima koristi od intervencijskog liječenja,[83] no najnoviji podaci ukazuju da bi se ono moglo odgoditi za najmanje 24 sata osim ako trajna klinička nestabilnost koja ne regira na inhibitore IIb/IIIa receptora ne zatraži žurniju strategiju. Stoga, u randomiziranoj usporedbi neposredne naspram odgođene PCI kod 251 pacijenata, 30-dnevna učestalost primarnog zajedničkog ishoda (smrt, ne-fatalni IM ili neplanirane revaskularizacije) je bila značajno viša u skupini koja je liječena neposredom intervencijom (60% naspram 39%).[84] Razlika je postojala i nakon 6-mjesečnog praćenja. Malo je vjerojatno da će odgađanje intervencije dulje od 96 sati biti od koristi, no podaci iz registra pokazuju da je ovo uobičajeno, naročito kod visokorizičnih pacijenata koji mogu imati najviše koristi od revaskularizacije.[85] Dokazi koji podupiru pravodobnu revaskularizaciju uvelike se temelje na PCI podacima, no za manji dio pacijenata je potrebno aortokoronarno premoštenje (CABG). Analiza podataka iz američ-

Non-ST-segment elevation myocardial infarction

NSTEMI has become the dominant mode of presentation for patients with AMI and in the recent analysis from Kaiser Permanente accounted for 66.9% of cases.[4] There has been a perception that NSTEMI is relatively benign despite evidence that prognosis after 2 months becomes substantially worse than with STEMI.[21,74] This may explain the tendency of doctors to under-treat NSTEMI based on a mismatch between perceived and actual risk that distorts management decisions, perpetuating the 'treatment-risk paradox'.[25] Thus, despite a worse prognosis, patients with NSTEMI are less likely than patients with STEMI to receive optimal secondary prevention treatment.[75] Moreover, in a study of 13,489 NSTEMI admissions recorded in the MINAP registry, invasive management was associated with better outcomes but was applied inequitably, with lower rates in high-risk groups, including older patients, women and those with cardiac comorbidities.[76]

Emergency management

Dual antiplatelet treatment with aspirin and clopidogrel is central to the management of NSTEMI.[77] The role of newer more potent ADP P2Y12 receptor blockers remains undetermined, although ticagrelor looks promising, based on its ability to reduce ischaemic events compared with clopidogrel in NSTEMI as well as STEMI, without increasing the risk of bleeding.[78] Simultaneous treatment with fondaparinux is now recommended in preference to enoxaparin, based on the findings in OASIS 5 which compared these agents in 20,078 patients with ACS.[79] Patients randomised to fondaparinux showed a 50% reduction in major bleeding compared with enoxaparin, with no difference in the incidence of ischaemic events. The reduction in bleeding risk was comparable whether clopidogrel or GPIIb/IIIa receptor blockers were co-prescribed[80] and cost-effectiveness has now been confirmed.[81] Indications for bivalirudin in NSTEMI have been harder to define and although it has a licence for use in combination with aspirin and clopidogrel, this is based principally on its safety profile (lower bleeding risk), its efficacy for reducing ischaemic events being no greater than either heparin plus GPIIb/IIIa receptor blocker or bivalirudin plus GPIIb/IIIa receptor blockers.[82]

The majority of patients with NSTEMI benefit from interventional management,[83] but recent data suggest this could be delayed for at least 24 h unless continuing clinical instability unresponsive to GPIIb/IIIa receptor blockers calls for earlier action. Thus, in a randomised comparison of immediate versus deferred PCI in 251 patients, the incidence at 30 days of the primary end point, a composite of death, non-fatal MI or unplanned revascularisation, was significantly higher in the group receiving immediate PCI (60% vs 39%).[84] The difference persisted at 6 months' follow-up. Delaying intervention beyond 96 h is unlikely to be helpful, yet registry data show that this is common, particularly in high-risk patients who have most to gain from revascularisation.[85] The evidence for timely revascularisation is largely based on PCI data but a small proportion of patients require coronary artery bypass grafting (CABG). An analysis of US registry data showed that the timing of CABG has no palpable effect on outcomes, the composite

kog registra je pokazala da vrijeme postupka CABG nije imalo zamjetan učinak na ishode, te su zajednički ishodi (smrt, IM, kongestivni srčano zatajivanje ili kardiogeni šok) bili slični (12,6% naspram 12,4%) bilo da je CABG obavljen unutar 48 sati od primitka ili kasnije.[86] Stoga se općenito rani kirurški zahvat preporuča kako bi se ograničio boravak u bolnici i smanjilo korištenje resursa.

Sekundarna prevencija

Kardiološka rehabilitacija

Dobrobit od kardiološke rehabilitacije kod 30.161 Medicare korisnika, od kojih je 20,5% nedavno doživjelo IM, potvrđena je snažnom povezanošću između prisustvovanja broju rehabilitacijskih programa i dugoročne učestalosti smrtnog ishoda i IM.[87] No trenutno izvješće o kardiološkoj rehabilitaciji u UK je ustanovilo da je uključeno svega 26% od podobnih pacijenata s IM, a stope pridržavanja terapije su od 65-85%.[88] Razlozi za loše prihvaćanje su složeni, a uključuju činjenicu da mnogi pacijenti ne žele sudjelovati u grupnim programima. Pregledni članak ukazuje da su i kućni programi jednako učinkoviti u poboljšanju kliničke i zdravstvene kvalitete života, a mnogim su pacijentima prihvatljiviji.[89] Troškovi zdravstvene skrbi su slični, a to podupire daljnju provedbu kućnih programa kardiološke rehabilitacije poput onih iz Birminghama.[90] Nedavan rezultat poboljšanog protoka krvi u miokardu zajedno s redukcijom u cirkulirajućim angiogenim citokinima kod pacijenata koji su podvrgnuti kardiološkoj rehabilitaciji pridaje uvjerenje da je kliničko poboljšanje poput fiziološkog.[91]

Promjene životnog stila

Važna komponenta kardiološke rehabilitacije je promjena životnog stila kako bi se zaštitilo od daljnjih koronarnih događaja. Na vrhu popisa je prestanak pušenja. Nedavna studija s uključenih 1.581 pacijenata praćenih 13 godina pokazala je da je prilagođeni omjer rizika za smrtni ishod od svih uzroka niži za 43% kod osoba koje su cijeli život nepušači i za 43% kod pacijenata koji su nakon IM prestali pušiti.[92] Novost je bila da kod ustrajnih pušača svako smanjenje od pet cigareta dnevno smanjuje rizik od smrti za 18%, što pruža određenu utjehu onim pacijentima kod kojih se potpuna apstinencija pokazala nemogućom. Čak i kod pacijenata koji su uspjeli prestati pušiti, ostaje opasnost od pasivne izloženosti dimu cigareta, što ukazuju podaci iz Škotske koji pokazuju da se prilagođeni mortalitet od svih uzroka i kardiovaskularni mortalitet kod osoba koje su preživjele IM i nisu nikad pušile povećava u skladu s izloženosti izmjerenim serumskim koncentracijama nikotina.[93] Poruka je jasna — zaštita od ponovljenih događaja kod osoba koje su preživjele IM zahtjeva prestanak pušenja od strane pacijenta te također od onih s kojima je pacijent u kontaktu, naročito članovi obitelji.

Zajedno s prestankom pušenja, savjeti vezani za tjelovježbu i dijetu koji se daju u službenim programima mogu imati pozitivan učinak na promjenjive čimbenike rizika, uključujući serumski kolesterol, arterijski tlak i indeks tjelesne mase.[94] Prehrambene preporuke obično uključuju suplemente omega-3 masnih kiselina95 no ovo je sada dovedeno u pitanje u nalazima dvije studije. U prvoj je 4.837

of death, MI, congestive heart failure, or cardiogenic shock being similar (12.6% vs 12.4%) whether CABG is done within 48 h of admission or later.[86] In general, therefore, early surgery is recommended to limit hospital stay and reduce resource use.

Secondary prevention

Cardiac rehabilitation

The benefit of cardiac rehabilitation among 30,161 Medicare beneficiaries, 20.5% of whom had recent MI, was confirmed by a strong dose-response relationship between the number of rehabilitation sessions attended and long-term rates of death and MI.[87] Yet a contemporary report of cardiac rehabilitation in the UK found that only 26% of eligible patients with MI are recruited, with adherence rates of 65-85%.[88] Reasons for the poor uptake are complex but include the fact that many patients do not want to participate in centre-based group programmes. A systematic review has now reported that home-based programmes are equally effective in improving clinical and health-related quality-of-life outcomes and are more acceptable to many patients.[89] Healthcare costs are similar, supporting the further provision of home-based cardiac rehabilitation such as that described by investigators in Birmingham.[90] The recent demonstration of improved myocardial blood flow plus reductions in circulating angiogenic cytokines in patients undergoing cardiac rehabilitation provides some reassurance that clinical improvement is physiologically based.[91]

Lifestyle modification

An important component of cardiac rehabilitation is lifestyle adjustment to help protect against further coronary events. Top of the list is smoking cessation. A recent study of 1,581 patients followed up for 13 years showed that the adjusted HR for all-cause mortality was lower by 43% in lifelong non-smokers and by 43% in patients who quit after MI.[92] A new finding was that among persistent smokers, each reduction of five cigarettes smoked per day reduced the risk of death by 18%, providing some comfort for those patients for whom complete abstinence proves impossible. Even among patients who mange to quit, there remains the hazard of second-hand smoke exposure, as reflected by data from Scotland showing that adjusted all-cause and cardiovascular mortality among never-smoking survivors of MI increases according to smoke exposure measured by serum cotinine concentration.[93] The message is clear that protection against recurrent events in survivors of MI requires smoking cessation by the patient and also by those with whom the patient makes contact, particularly family members.

Together with smoking cessation, advice about exercise and diet delivered in formal programmes can have a salutary effect on modifiable risk profiles, including serum cholesterol, blood pressure and body mass index.[94] Dietary recommendations usually include omega-3 fatty acid supplements[95] but this has now been questioned by the findings of two studies. In the first, 4,837 patients with previous MI were randomised to margarines containing marine

pacijenata s prethodnim IM randomizirano na margarine koji sadrže morske n-3 masne kiseline i alfa-linoleinsku kiselinu iz biljaka u faktorskom dizajnu 2 2.[96] Učestalost neželjenih kardiovaskularnih događaja se nije razlikovala značajno među analiziranim skupinama. U drugoj studiji su visoko pročišćene omega-3 masne kiseline nasumično primjenjene 3,851 pacijentu s AIM u praćenju koje je trajalo 12 mjeseci.[97] Nije bilo značajne razlike u učestalosti iznenadne srčane smrti (1,5% naspram 1,5%), ukupnom mortalitetu (4,6% naspram 3,7%), ili velikim neželjenim cerebrovaskularnim ili kardiovaskularnim događajima (10,4% naspram 8,8%) između aktivno liječene i placebo skupine. Rezultati ove dvije studije čine preporuke za sekundarnu prevenciju sa suplementima omega-3 masnih kiselina nakon IM teško održivima.

Farmakoterapija

Važnost optimalne sekundarne prevencije nakon IM je naglašena u modeliranoj studiji u kojoj je veća apsolutna dobrobit za preživljavanje ostvarena optimizacijom liječenja u sekundarnoj prevenciji u usporedbi s reperfuzijskim liječenjem u bolnici (104 nasuprot ≥30 života/ 10.000).[98] Preporuke su ASK, beta blokatori, statini, blokatori renin-angiotenzinskog sustava i tienopiridini — studija s uključenih 5.353 pacijenata pokazuje da je liječenje sa svih pet lijekova smanjilo jednogodišnji mortalitet za 74% u usporedbi s liječenjima s jednim lijekom ili bez ijednog lijeka, uz dosljedne učinke na STEMI i NSTEMI.[75] Dokaz da statini i klopidogrel daju najveću nezavisnu farmakološku dobrobit (OR za smrtni ishod 0,85 (0,73 do 0,99) i 0,84 (0,72 do 0,99)) su dali istraživači GRACE studije sa 5.148 pacijenata s AKS,[99] a dvije zasebne studije su sada izvijestile o štetnim posljedicama nepridržavanja liječenja s ovim lijekovima tijekom prve godine nakon otpusta iz bolnice.[100,101] Poruka je jasna — propisivanje terapije za sekundarnu prevenciju u skladu sa smjernicama i promoviranje pridržavanja uputa za liječenje mogu zajedno dovesti do daljnjeg smanjenja mortaliteta kod pacijenata s IM.

Implatibilni kardioverter-defibrilatori (ICD)

Ejekcijska frakcija lijeve klijetke (LVEF) nakon AIM ostaje predvidljiva za iznenadnu smrt i u razdoblju liječenja primarnom PCI[102] te je ključna varijabla za određivanje kojim pacijentima bi trebalo ponuditi implatibilni kardioverter-defibrilator (ICD) u primarnoj prevenciji.[103] Međutim, LVEF u akutnoj fazi predstavlja nepouzdan vodič za LVEF nakon 3 mjeseca, kada često nastupi značajan oporavak kontrakcijske funkcije. Postoji još jedan razlog za odgodu odluke o ICD dulje od preporučenih 40 dana. Nedavna randomizirana studija s primjenom ICD u liječenju 898 pacijenata s LVEF ≥40%, koji su uključeni unutar 31 dana od AIM, nije pokazala ukupno smanjenje mortaliteta za pacijente koji su primili ICD jer je visoka učestalost iznenadne smrti poništila zaštitu od iznenadne aritmijske smrti koju pruža ICD.[104] Sekundarna analiza studije DINAMIT je potvrdila visok rizik neiznenadne smrti kod pacijenata koji prime ICD rano nakon infarkta miokarda, dok su ispitivači studije VALIANT izvijestili da su ponovljeni infarkt ili ruptura srca česti uzroci smrti tijekom ovog razdoblja.[105,106] Sve spomenuto objašnjava zašto ICD ne pruža zaštitu od smrti

n-3 fatty acids and plant-derived alpha-linolenic acid in a 2 2 factorial design.[96] The rate of adverse cardiovascular events did not differ significantly among the study groups. In the second study, highly purified omega-3 fatty acids were randomly allocated to 3,851 patients with AMI followed up for 12 months.[97] There were no significant differences in rates of sudden cardiac death (1.5% vs 1.5%), total mortality (4.6% vs 3.7%), or major adverse cerebrovascular and cardiovascular events (10.4% vs 8.8%) between treatment and placebo groups. The results of these two trials make recommendations for secondary prevention with omega-3 fatty acid supplements after MI difficult to sustain.

Pharmacotherapy

The importance of optimal secondary prevention after MI was emphasised in a modelling study, in which greater absolute gains in survival were achieved by optimising secondary prevention treatments compared with in-hospital reperfusion treatments (104 vs ≥30 lives/10,000).[98] Recommended are aspirin, beta blockers, statins, renin-angiotensin system blockers and thienopyridines — a study of 5,353 patients showing that treatment with all five drugs reduced 1-year mortality by 74% compared with treatment with one or none of them, with consistent effects in STEMI and NSTEMI.[75] Evidence that statins and clopidogrel provide the greatest independent pharmacological benefit (ORs for death 0.85 (0.73 to 0.99) and 0.84 (0.72 to 0.99)) was provided by the GRACE investigators in a nested case-control study of 5,148 patients with ACS,[99] and two separate studies have now reported the adverse consequences of failing to adhere to treatment with these drugs during the first year after discharge.[100,101] The message is clear that prescribing secondary prevention treatment according to guideline recommendations and promoting adherence to treatment can together produce further mortality reductions in patients with MI.

Implantable cardioverter-defibrillators (ICDs)

Left ventricular ejection fraction (LVEF) after AMI remains predictive of sudden death in the primary PCI era[102] and is the key determinant of which patients should be offered an ICD for primary prevention.[103] However, LVEF in the acute phase is an unreliable guide to LVEF at 3 months when significant recovery of contractile function has often occurred. But there is another reason for delaying decisions about ICDs beyond the guideline-recommended 40 days. Thus a recent randomised trial of ICD therapy in 898 patients with LVEF ≥40%, recruited within 31 days of AMI, showed no overall mortality reduction for the patients who received an ICD because a high rate of non-sudden death negated protection against sudden arrhythmic death provided by the ICD.[104] A secondary analysis of DINAMIT has now confirmed a high risk of non-sudden death in patients who receive ICDs early after MI, while the VALIANT investigators have reported that recurrent infarction or cardiac rupture are common causes of death during this period.[105,106] Taken together, these findings explain why ICDs fail to protect against death if implanted early after MI. Decisions should, therefore, be deferred, and patients selec-

ako se implantira rano nakon IM. Odluku bi stoga trebalo odgoditi, a pacijente za terapiju ICD odabrati prema mjerenjima LVEF nakon 40 dana.

Zaključak

Liječenje AKS se nastavlja razvijati i poboljšavati. Izazov za kardiovaskularne istraživače je kako održati ovaj zamah i osigurati da poboljšanja ishoda koja su uočena u razvijenom svijetu imaju globalan učinak.

ted for ICD therapy according to measurement of LVEF at 40 days.

Conclusion

The management of ACS continues to evolve and improve. The challenge for cardiovascular researchers is to maintain this momentum and to ensure that the improvements in outcome seen in the developed world have a global impact.

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*Address for correspondence: London Chest Hospital, NIHR Cardiovascular Biomedical Research Unit,

London, E2 9JX, UK

E-mail: charles.knight@bartsandthelondon.nhs.uk

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