

# Almanah 2015.: Koronarna bolest srca

## Almanac 2015: coronary artery disease

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**SAŽETAK:** Posljednjih se godina prati veliki napredak u dijagnostici i liječenju bolesnika sa koronarnom bolesti srca (KBS). To uključuje primjenu novih biomarkera i metoda slikovnog prikaza u bolesnika s povišenim rizikom za nastanak KBS-a, zbrinjavanje akutnog infarkta miokarda s elevacijom ST segmenta, nove uređaje za liječenje angine refraktorne na terapiju lijekovima, uporabu nestatinskih hipolipemika, bolje razumijevanje rizika i prednosti dugoročne dvojne antitrombotične terapije te uporabu novih antitrombotičnih lijekova. U ovome su članku sažeta istraživanja vezana za KBS objavljena u časopisu *Heart* tijekom 2014. i 2015. godine, u skladu s člancima objavljenima u drugim vodećim kardiovaskularnim časopisima.

**SUMMARY:** Recent years have seen major advances in the evaluation and treatment of patients with coronary artery disease. These include assessment of novel biomarkers and imaging methods for patients at risk for coronary artery disease, care of patients with ST-segment elevation myocardial infarction, a novel device to treat medical refractory angina, use of non-statin lipid-lowering agents, a better understanding of the risks and benefits of longterm dual antiplatelet therapy and the use of the newer antiplatelet agents. This article summarises research related to coronary artery disease published in *Heart* in 2014 and 2015, within the context of other major cardiovascular journals.

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### Epidemiologija

Kardiovaskularne bolesti (KVB) i dalje su vodeći uzrok smrti u industrijaliziranim zemljama.<sup>1,2</sup> Postoje razlike u zastupljenosti po spolu, pa su tako u 2012. godini KVB bile glavni uzrok smrti žena u Ujedinjenom Kraljevstvu, dok su za muškarce to bile maligne bolesti (**slika 1**).<sup>3</sup> Wilmot *i sur.* nedavno su objavili da je smrtnost zbog KVB-a u Sjedinjenim Američkim Državama u padu u dobnoj skupini starijih od 25 godina. Ipak, primijećena je razlika u brzini smanjenja smrtnosti ovisno o životnoj dobi, pri čemu je u osoba mlađih od 55 godina zamijećena manja relativna stopa pada nego u starijim dobnim skupinama.<sup>4</sup>

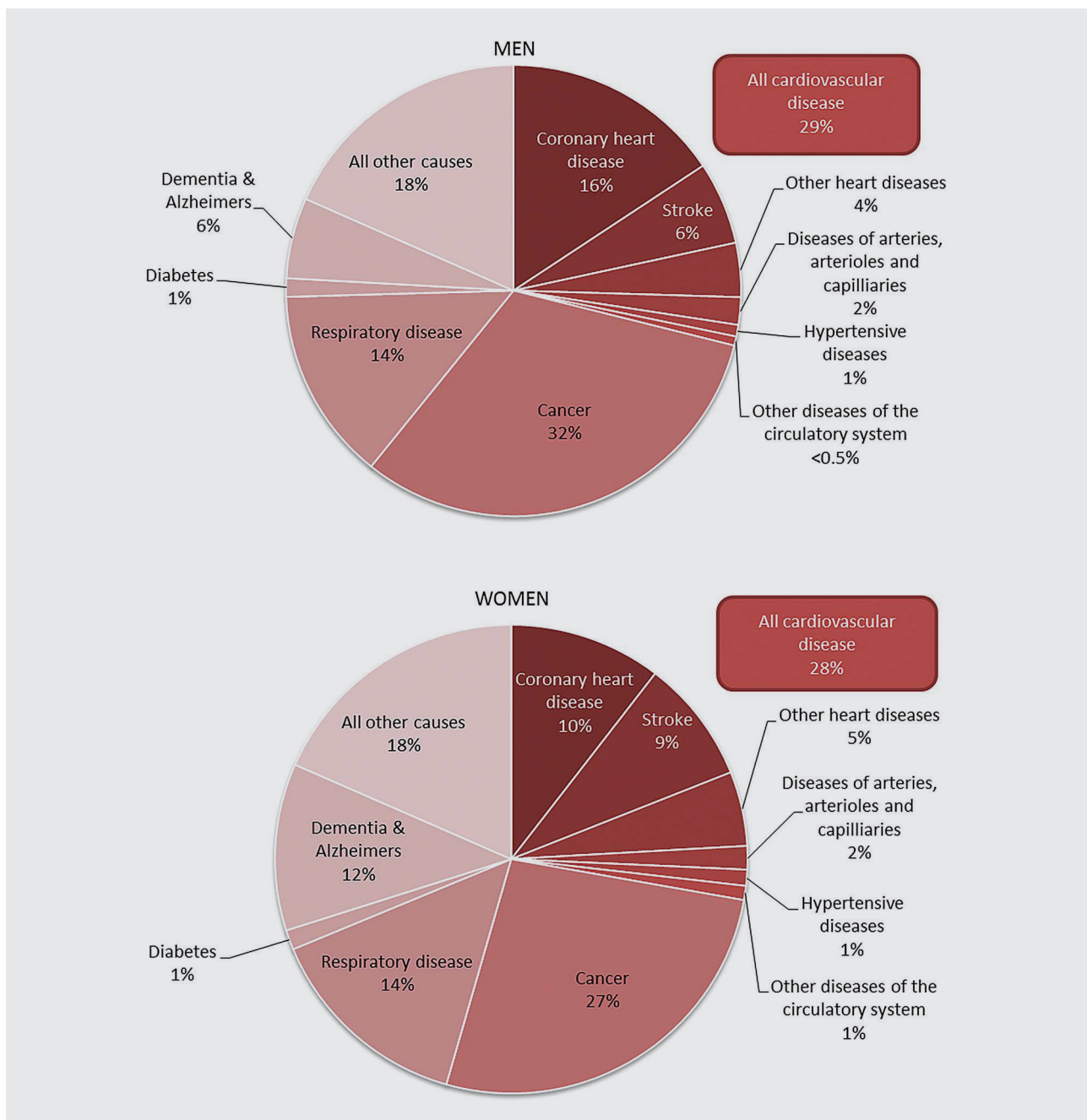
### Epidemiology

Cardiovascular disease (CVD) remains the main cause of death within industrialised nations.<sup>1,2</sup> Gender differences exist, and in 2012, CVD was the main cause of death for women within the UK; however, for men, cancer was the main cause of death (**Figure 1**).<sup>3</sup> Wilmot et al recently reported that mortality secondary to CVD has fallen for adults over the age of 25 years within the USA. However, variation was seen between the rate of fall for various age groups with those <55 years experiencing a smaller relative decrease than older age groups.<sup>4</sup>

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**FIGURE 1. Deaths by cause and sex, UK.** This figure compiles data from the four countries of the UK. In Northern Ireland, the data for lung cancer only includes International Classification of Diseases-10 code C34. Adapted from England and Wales, Office for National Statistics (2014) Deaths registered by cause, sex and age. <http://www.statistics.gov.uk> (accessed January 2014); Scotland, National Records of Scotland (2014) Deaths, by sex, age and cause. <http://www.gro-scotland.gov.uk> (accessed January 2014); Northern Ireland, Statistics and Research Agency (2014) Registrar General Annual Report. NISRA: Belfast. Figure 1 from Bhatnagar et al.<sup>3</sup>

## Procjena kardiovaskularnog rizika

Iako su tradicionalni čimbenici kardiovaskularnog rizika korisni pri procjeni budućih kardiovaskularnih događaja za pojedinca, najnovije studije usmjerile su se na novije čimbenike rizika i/ili metode slikovnog prikaza radi poboljšanja procjene rizika. Kalcifikacije aortnog zalistka smatraju se manifestacijom sustavne ateroskleroze te u asimptomatskih osoba mogu upućivati na povećani rizik od budućih kardiovasku-

## Cardiovascular risk assessment

Although traditional cardiovascular risk factors are useful in evaluating an individual's risk for future cardiovascular events, contemporary studies have focused on novel risk factors and/or imaging methods in an attempt to improve this risk assessment. Aortic valve calcium is thought to be a manifestation of systemic atherosclerosis and may therefore identify asymptomatic individuals at a higher risk for future

larnih događaja. Koristeći se podacima iz istraživanja *Heinz Nixdorf Recall Study*, Kalsch *i sur.*<sup>5</sup> analizirali su 3944 asimptomatska pojedinca kojima su oslikavanjem CT-om izmjerili vrijednost kalcifikacije na aortnom zalistku. Tijekom razdoblja praćenja od 9 godina i nakon usklađivanja s tradicionalnim čimbenicima rizika po Framinghamu, osobe s vrijednosti kalcifikacija na aortnom zalistku > 0 imali su mnogo veći rizik od budućih kardiovaskularnih događaja. Kada su u obzir uzeti vrijednosti kalcifikacija koronarnih arterija i čimbenici rizika po Framinghamu, prisutnost kalcifikacija na aortnom zalistku više nije bila neovisni prediktor kardiovaskularnih događaja. Širina distribucije volumena eritrocita (RDW) mjera je razlike u veličini eritrocita koja se smatra novim biljekom za bolesnike s raznim oblicima koronarne bolesti srca (KBS).<sup>6,7</sup> Borne *i sur.*<sup>8</sup> analizirali su više od 28 000 osoba bez prijašnjih KVB-a te otkrili da je veća vrijednost RDW-a povezana s povećanim rizikom od budućih akutnih koronarnih događaja. Pozivajući se na pretpostavku da ateroskleroza dijeli mnoga obilježja s drugim upalnim bolestima, Hsiao *i sur.*<sup>9</sup> analizirali su pacijente s kroničnim osteomijelitisom kako bi utvrdili imaju li povećani rizik od kasnijih KVB-a. Koristili su se podacima državnoga zdravstvenog osiguranja kod više od 15 000 pacijenata s osteomijelitisom te otkrili da je u pojedinaca s osteomijelitisom incidencija KVB-a 1,65 puta veća nakon korekcije za čimbenike kardiovaskularnog rizika. Ipak, potencijalni mehanizmi koji povezuju osteomijelitis i kasniji nastanak KVB-a i dalje su otvoreni.

## Stabilna koronarna bolest srca

### ANTITROMBOCITNA TERAPIJA

Bolesnici s poznatom KBS imaju trajno povećani rizik od budućih kardiovaskularnih događaja usprkos medikamentnoj terapiji. Dosadašnje studije o dugoročnoj uporabi tienopiridina u bolesnika s poznatom KBS nisu pokazale pozitivan učinak.<sup>10</sup> Bolesnici s implantiranim stentom koji izlučuje lijek (DES) čine podskupinu bolesnika s poznatom KBS koju uobičajeno susrećemo u svakodnevnoj kliničkoj praksi. Takvi pacijenti imaju pridružen, premda nizak, rizik od kasne tromboze stenta i rizik od budućih kardiovaskularnih događaja. Primjena dvojne antitrombotične terapije (DAPT) duže od uobičajenih 12 mjeseci može smanjiti broj budućih kardiovaskularnih događaja, no nastavak primjene povezan je s povećanim rizikom od krvarenja. U *DAPT* studiji praćeno je više od 9000 pacijenata s DES-om koji su nakon jedne godine liječenja randomizirani u skupine koje su primale ili tienopiridin ili placebo, uz nastavak liječenja acetilsalicilatnom kiselinom.<sup>11</sup> U skupini koja je nastavila uzimati tienopiridin rizik od tromboze stenta i velikih nepovoljnih kardiovaskularnih i cerebrovaskularnih događaja bio je smanjen u usporedbi sa skupinom liječenom placebom. S druge strane, umjereni ili teški slučajevi krvarenja bili su češći u skupini koja je nastavila uzimati tienopiridin. *ARCTIC-Interruption* istraživanje na sličan je način randomiziralo 1259 pacijenata nakon jedne godine u skupine koje su liječene tienopiridinom ili placebom te dokazalo sličnu pojavnost kardiovaskularnih događaja, uz veći broj krvarenja u skupini na tienopiridinu.<sup>12</sup> Prema postojećoj literaturi, preporučuje se procijeniti rizik i prednosti na-

cardiovascular events. Using data from the *Heinz Nixdorf Recall Study*, Kalsch *et al*<sup>5</sup> evaluated 3944 asymptomatic individuals and measured aortic valve calcium using CT. Over a mean follow-up period of approximately 9 years and after adjusting for traditional Framingham risk factors, those with an aortic valve calcium score >0 had a significantly increased risk for future CVD events. However, when including coronary artery calcium and traditional Framingham risk factors, the presence of aortic valve calcium no longer independently predicted CVD events. Red cell distribution width is a measure of the size variation of red blood cells and is thought to be a novel marker for patients with various manifestations of coronary artery disease (CAD).<sup>6,7</sup> Borne *et al*<sup>8</sup> evaluated over 28 000 subjects free of prior CVD and found that a high red cell distribution width was associated with an increased risk for future acute coronary events. Given the premise that atherosclerosis shares many features of other inflammatory diseases, Hsiao *et al*<sup>9</sup> evaluated patients with chronic osteomyelitis to determine if they had an increased risk for subsequent CVD. Using a national insurance dataset with over 15 000 patients with osteomyelitis, the authors found that the incident rate of CVD was 1.65 times higher, after controlling for cardiovascular risk factors, in those individuals with osteomyelitis. The potential mechanisms linking osteomyelitis and subsequent CVD remain unclear.

## Stable CAD

### ANTIPLATELET THERAPY

Patients with established CAD have an ongoing risk for future cardiovascular events, despite the use of medical therapy. Prior studies evaluating long-term thienopyridine use in patients with established CVD failed to show a benefit.<sup>10</sup> In routine clinical practice, a commonly encountered subgroup of patients with established CAD are those with a prior coronary drug eluting stent (DES). These patients have an inherent, although low, risk for late stent thrombosis and future cardiovascular events. Continuing dual antiplatelet therapy (DAPT) beyond the traditional 12 months may reduce future cardiovascular events; conversely, continued DAPT may be associated with an increased risk of bleeding. The DAPT study evaluated over 9000 patients with a DES and at 1 year randomised patients to continued thienopyridine treatment or placebo in the setting of continued aspirin therapy.<sup>11</sup> In those receiving continued thienopyridine treatment, the risk of stent thrombosis and major adverse cardiovascular and cerebrovascular events was reduced compared with those receiving placebo. However, moderate or severe bleeding events were increased in those receiving continued thienopyridine treatment. The *ARCTIC-Interruption* trial randomised 1259 patients after 1 year in a similar manner to the DAPT study to continued thienopyridine treatment or placebo and found similar cardiovascular events with increased bleeding events in those receiving thienopyridine treatment.<sup>12</sup> The current literature supports weighing the risks versus benefits of continued thienopyridine treatment after 1 year and individualising treatment recommendations based upon specific patient-related factors.<sup>13</sup>

**TABLE 1. Comparison of non-invasive imaging modalities table 2 from Yilmaz et al<sup>19</sup>.**

	Stress echocardiography	SPECT/PET	Stress-CMR	Coronary CT
Time to perform the test	30–45 min	Image acquisition 5–8 min with new cameras (1 d protocol at 6 mSv total effective dose); total time ~45 min	40–50 min (including functional and morphological imaging)	<1 min
Special equipment	No (apart from an appropriate ultrasound system)	Yes (SPECT/PET camera+specific tracer)	Yes (MR scanner+contrast agent)	Yes (appropriate CT scanner +contrast agent)
Sensitivity versus specificity	80%–85% vs 80%–88% (not corrected for referral bias)	90%–91%/81%–97% vs 75%–84%/74%–91% (sensitivity 51% and 71% in women and men, respectively, in study without referral bias)	67%–94% vs 61%–85% (sensitivity 89% and 86% in woman and men, respectively, in study without referral bias)	95%–99% vs 64%–83%
Operator experience	Highly important for high diagnostic yield	Important in performing the test (although automated analysis is feasible)	Important in assessing ischaemic regions and excluding artefacts	Important in assessing stenoses and excluding artefacts
Major advantages	<ul style="list-style-type: none"> <li>▶ Wide availability</li> <li>▶ Low costs</li> <li>▶ High spatial and temporal resolution</li> <li>▶ No radiation burden</li> <li>▶ Feasible in case of advanced renal disease</li> <li>▶ Feasible in patients with devices</li> <li>▶ High diagnostic specificity and functional predictive value</li> </ul>	<ul style="list-style-type: none"> <li>▶ Wide availability (SPECT)</li> <li>▶ Feasible in patients with dyspnoea</li> <li>▶ Feasible in case of advanced renal disease</li> <li>▶ Feasible in patients with devices</li> <li>▶ High diagnostic sensitivity (particularly PET)</li> </ul>	<ul style="list-style-type: none"> <li>▶ High spatial and temporal resolution</li> <li>▶ Images in all axes possible</li> <li>▶ No windowing limitation</li> <li>▶ No radiation burden</li> <li>▶ Multiparametric imaging with acquirement of functional and structural parameters</li> <li>▶ High diagnostic sensitivity and specificity</li> </ul>	<ul style="list-style-type: none"> <li>▶ Wide availability</li> <li>▶ Highest spatial and temporal resolution</li> <li>▶ Direct visualisation of plaques and stenoses</li> <li>▶ Feasible in patients with devices</li> <li>▶ High diagnostic sensitivity and high negative predictive value</li> </ul>
Major disadvantages	<ul style="list-style-type: none"> <li>▶ Poor acoustic window in some patients</li> <li>▶ High intraobserver and interobserver variability</li> <li>▶ Difficult assessment of infarcted segments</li> <li>▶ Possible side effects of dobutamine in DSE</li> </ul>	<ul style="list-style-type: none"> <li>▶ Radiation burden</li> <li>▶ Cost intensive</li> <li>▶ Low spatial resolution</li> <li>▶ Lower specificity than DSE or stress CMR</li> <li>▶ Possible side effects/contraindications of adenosine</li> <li>▶ Diaphragmatic attenuation artefacts in the inferior LV wall</li> </ul>	<ul style="list-style-type: none"> <li>▶ Cost intensive</li> <li>▶ Restricted in case of advanced renal disease</li> <li>▶ Not feasible in patients with devices</li> <li>▶ Patient breath-hold required</li> <li>▶ Possible side effects/contraindications of adenosine/dobutamine</li> <li>▶ Sinus rhythm helpful</li> </ul>	<ul style="list-style-type: none"> <li>▶ Radiation burden</li> <li>▶ Cost intensive</li> <li>▶ Restricted in case of advanced renal disease</li> <li>▶ Only anatomic data, limited functional data</li> <li>▶ Not helpful in case of severe coronary calcification</li> <li>▶ Sinus rhythm and low heart frequency required</li> </ul>

CMR, cardiovascular magnetic resonance; DSE, dobutamine stress echocardiography; LV, left ventricular; MR, magnetic resonance; PET, positron emission tomography; SPECT, single photon emission CT.

stavka liječenja tienopiridinom nakon godine dana te prilagoditi preporuke o liječenju prema individualnim čimbenicima rizika pojedinog bolesnika.<sup>13</sup>

## NEINVAZIVNO DIJAGNOSTIČKO TESTIRANJE

Postoji niz neinvazivnih slikovnih dijagnostičkih metoda koje su nam na raspolaganju pri procjeni bolesnika sa sumnjom na angiozni bol u prsima.<sup>14</sup> Prednosti i ograničenja svake od tih metoda saželi su Yilmaz i Sechtem (tablica 1).<sup>15,16</sup> Posljednjih je godina kardiovaskularna magnetna rezonancija (MR) doživjela najveći napredak, a dijagnostička preciznost pri dijagnozi opstruktivne KBS uporabom magnetne rezonancije snage polja 3T sad je usporediva s jednofotonskom emisijom kompjutoriziranom tomografijom.<sup>17</sup>

## MJERENJE FRAKCIJSKE REZERVE PROTOKA

Mjerenje frakcijske rezerve protoka (FFR) invazivan je postupak kojim se određuje hemodinamska važnost angiografski umjerenih lezija na koronarnim arterijama.<sup>18</sup> Randomizirana su istraživanja pokazala da uporaba FFR-a smanjuje primjenu nepotrebnih perkutanih koronarnih intervencija (PCI) i budućih kardiovaskularnih događaja u usporedbi s temeljenjem odluka isključivo po nalazu koronarne angiografije.<sup>19</sup> Usprkos tim dobrobitima, uporaba FFR-a u svakodnevnoj kliničkoj praksi relativno je rijetka, vjerojatno zbog povećanih troškova i potrebe dodatnog vremena za mjerenja koja zahtijevaju pozicioniranje mjerne žice distalno od stenozе u koronarnoj žili. Zhang *i sur.*<sup>20</sup> proveli su metaanalizu koja je uključivala četiri prospektivne i tri retrospektivne studije

## NON-INVASIVE DIAGNOSTIC TESTING

A variety of non-invasive imaging methods are available to evaluate patients with presumed anginal chest pain.<sup>14</sup> The advantages and limitations of each of these non-invasive imaging methods were summarised by Yilmaz and Sechtem (Table 1).<sup>15,16</sup> In recent years, cardiovascular MRI has experienced the most robust growth and the diagnostic accuracy for identifying obstructive CAD using 3.0 T magnetic resonance scanners is now comparable with single photon emission CT.<sup>17</sup>

## FRACTIONAL FLOW RESERVE

Fractional flow reserve (FFR) provides an invasive means to determine the haemodynamic significance of moderate coronary artery lesions.<sup>18</sup> Randomised trials have shown that use of FFR (FFR-guided) compared with solely relying on the results of coronary angiography (angiography-guided) reduces the need for unnecessary percutaneous coronary intervention (PCI) and decreases future cardiovascular events.<sup>19</sup> Despite these benefits, the adoption of FFR into routine clinical practice has been relatively low likely related to issues of cost and the additional time required to perform FFR measurements as this requires placement of a guidewire to the distal coronary bed. To provide additional information regarding the benefits of FFR, Zhang *et al*<sup>20</sup> performed a meta-analysis that included four prospective and three retrospective studies with over 49 000 patients. An FFR-guided PCI strategy was associated with a 70% relative reduction in major adverse



s više od 49 000 pacijenata kako bi došli do novih podataka o prednostima primjene FFR-a. Primjena strategije FFR-om vođene PCI povezana je sa 70 %-tnim smanjenjem velikih neželjenih kardiovaskularnih događaja (MACE) u usporedbi s intervencijama vođenima angiografskim nalazom. Ova metaanaliza daljnja je potpora rutinskoj uporabi FFR-a u slučajevima granične stenozе koronarne arterije tijekom moguće PCI intervencije.

### ANGINA REFRAKTORNA NA LIJEKOVE

Liječenje pacijenata s refraktornom anginom i dalje je izazov.<sup>21</sup> Uspriko primjeni nove antianginalne terapije (ranolazin) velik broj pacijenata ima prisutne značajne simptome i smanjenu kvalitetu života. Verheye *i sur.* nedavno su istražili primjenu novog uređaja sa širećim balonom koji se postavlja u koronarni sinus da bi se postiglo fokalno suženje, što povećava tlak unutar koronarnog sinusa te teoretski dovodi do preraspodjele krvi prema ishemičnom miokardu.<sup>22,23</sup> U malom kliničkom ispitivanju u 104 pacijenta s III. ili IV. stupnjem angine prema Kanadskom kardiovaskularnom društvu uporaba tog uređaja bila je povezana sa znatnim poboljšanjem stupnja angine u usporedbi s placebo.

### VAZOSPASTIČNA ANGINA

Blokatori kalcijских kanala čine skupinu lijekova koja čini temelj liječenja vazospastične angine. No, u 20 % pacijenata ovakvo liječenje može biti neučinkovito i/ili popraćeno nuspojavama. Istraživanje STELLA uključilo je 50 pacijenata s vazospastičnom anginom koji su imali prisutne simptome usprkos liječenju amlodipinom. Pacijenti su bili randomizirani

cardiovascular events (MACE) compared with an angiography-guided PCI strategy. This meta-analysis provides further evidence to support the routine use of FFR in the setting of intermediate coronary artery stenosis in patients being considered for PCI.

### MEDICALLY REFRACTORY ANGINA

The treatment of patients with medical refractory angina remains challenging.<sup>21</sup> Despite the use of newer antianginal therapy (ranolazine), a large number of patients remain highly symptomatic with impaired quality of life. Verheye *et al* recently reported the use of a novel balloon-expandable device placed within the coronary sinus to cause of a focal narrowing, thereby increasing pressure within the coronary sinus and theoretically redistributing blood flow to ischaemic myocardium.<sup>22,23</sup> In a small clinical trial of 104 patients with Canadian Cardiovascular Society (CCS) class III or IV angina, use of the device relative to a sham procedure was associated with a marked improvement in CCS angina class.

### VASOSPASTIC ANGINA

Although calcium channel blockers are the mainstay of therapy for patients with vasospastic angina, up to 20% of patients may be refractory to treatment and/or experience side effects. The Study to evaluate the Efficacy and safety of Pletaal (cilostazol) in subjects with vasospastic angina (STELLA) trial included 50 patients with significant vasospastic angina who remained symptomatic despite amlodipine therapy and randomised them to cilostazol or placebo for 4 weeks.<sup>24</sup> Patients receiving cilostazol therapy had a significant reduction in weekly angina episodes compared with those receiving placebo, 66% vs 18%,  $p=0.0009$ , respectively (Figure 2).

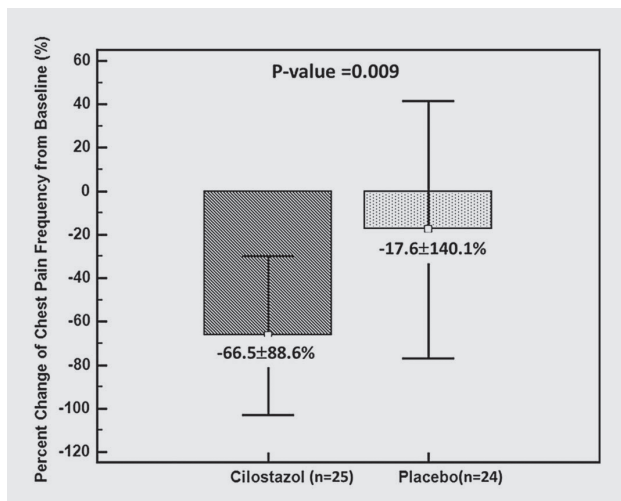
### DIABETES MELLITUS AND MULTIVESSEL CAD

Diabetes mellitus is an independent predictor for worse outcome following coronary revascularisation.<sup>25,26</sup> In addition, the extent of revascularisation (complete vs incomplete) is also thought to be extremely important in the setting of diabetes mellitus.<sup>27,28</sup> Jimenez-Navarro included over 5000 patients with multivessel CAD undergoing PCI and evaluated the association of diabetes mellitus and complete versus incomplete revascularisation on long-term outcome.<sup>29</sup> Complete revascularisation was associated with significantly improved survival over 10 years (Figure 3). More importantly, patients with diabetes mellitus and incomplete revascularisation had a significantly lower survival compared with their non-diabetic counterparts. These findings suggest that the extent of revascularisation is particularly important in the setting of diabetes mellitus and complete revascularisation should be a goal of therapy.

### Acute coronary syndromes

#### USE OF THROMBECTOMY

The large-scale randomised Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) trial showed a benefit of routine thrombectomy prior to coronary stenting with improved my-



**FIGURE 2.** Box-and-whiskers plots showing percentage change of weekly chest pain frequency. Chest pain frequency was significantly improved in the cilostazol group compared to the placebo group. Primary endpoint was defined as: (number of angina episodes at baseline week – number of angina episodes at last week)/(number of angina episodes at baseline week)×100. The distribution range signifies the 95% CIs. Mean, rank-ANCOVA with treatment as factor and baseline as covariate ( $p<0.05$ ). Figure 2 from Shin *et al.*<sup>24</sup>

rani u skupine liječene cilostazolom ili placeboom tijekom 4 tjedna.<sup>24</sup> U pacijenata koji su liječeni cilostazolom zamijećeno je znatno smanjenje broja angioznih napadaja tjedno u usporedbi s placeboom: 66 % prema 18 %,  $p = 0,0009$  (slika 2).

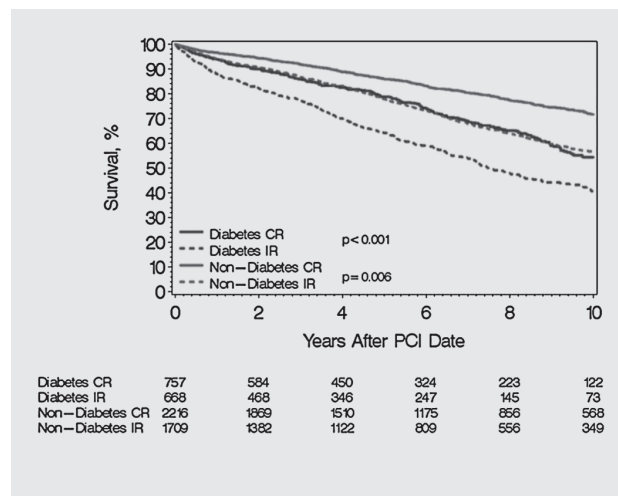
## DIJABETES I VIŠEŽILNA KORONARNA BOLEST SRCA

Dijabetes je neovisni prediktor nepovoljnijih ishoda nakon koronarne revaskularizacije.<sup>25,26</sup> Usto, smatra se i da je opseg revaskularizacije (potpuna ili nepotpuna) također vrlo važan u dijabetičara.<sup>27,28</sup> Jimenez-Navarro *i sur.* proveli su istraživanja u više od 5000 pacijenata koji su liječeni s pomoću PCI-ja zbog višežilne KBS kako bi utvrdili ovisnost dugoročnih ishoda o dijabetesu i potpunoj ili nepotpunoj revaskularizaciji.<sup>29</sup> Potpuna revaskularizacija bila je povezana s poboljšanom desetogodišnjom stopom preživljenja (slika 3), a još je važnije da su pacijenti s dijabetesom i nepotpunom revaskularizacijom imali mnogo manju stopu preživljenja u usporedbi s onima bez dijabetesa. Ovi rezultati upućuju na to da je opseg revaskularizacije posebice važan u dijabetičara, u kojih bi cilj liječenja trebala biti potpuna revaskularizacija.

## Akutni koronarni sindrom

### PRIMJENA TROMBEKTOMIJE

Velika randomizirana studija TAPAS pokazala je pozitivne učinke rutinske trombektomije prije ugrađivanja koronarnog stenta u smislu poboljšanog stupnja miokardijalnog punjenja i smanjene smrtnosti.<sup>30,31</sup> Nakon objavljivanja studije TAPAS vodeća američka i europska (*American College of Cardiology, American Heart Association, Society Cardiac Angiography and Intervention i European Society of Cardiology*) stručna društva u svojim su smjernicama preporučili rutinsku primjenu trombektomije tijekom primarne PCI kod akutnog infarkta miokarda s elevacijom ST segmenta.<sup>32,33</sup> No, istraživanje TASTE nije dokazalo pozitivne učinke rutinske trombektomije nakon jedne godine praćenja.<sup>34</sup> Metaanaliza 17 kliničkih ispitivanja s uključenih više od 20 000 pacijenata također nije pronašla pozitivne učinke rutinske trombektomije.<sup>35</sup> U pokušaju da razriješe te proturječne rezultate, Jolly *i sur.*<sup>36</sup> proveli su istraživanje TOTAL u 10 732 pacijenta tako-



**FIGURE 3. Unadjusted mortality curves during follow-up for stable disease versus acute coronary syndrome (ACS). CR, complete revascularisation; IR, incomplete revascularisation; PCI, percutaneous coronary intervention. Figure 1 from Jimenez-Navarro et al.<sup>29</sup>**

oacardial blush grade and lower mortality.<sup>30,31</sup> Following publication of the TAPAS trial, American College of Cardiology/American Heart Association/Society Cardiac Angiography and Intervention (ACC/AHA/SCAI) and European Society of Cardiology practice guidelines thus recommended the routine use of thrombectomy during primary PCI for ST-segment elevation myocardial infarction (STEMI).<sup>32,33</sup> In contrast, the Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) trial found no benefit of routine thrombectomy at 1 year.<sup>34</sup> A meta-analysis of 17 trials with over 20 000 patients also failed to document a benefit of routine thrombectomy.<sup>35</sup> In an attempt to address these conflicting results, Jolly et al.<sup>36</sup> enrolled 10 732 patients in the Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) and found no reduction in cardiovascular events for patients randomised to routine thrombectomy. In addition, the occurrence of stroke, and in particular ischaemic stroke, was higher in patients receiving thrombectomy<sup>37</sup> (Table 2). At the present time, the

**TABLE 2. Summary of clinical trials evaluating the use of thrombectomy for ST-segment elevation myocardial infarction.**

Study name/author year	n	Study design	Primary endpoint	Findings
TAPAS 2008	1071	Randomised	Cardiac death or non-fatal myocardial infarction at 1 year	Reduction in cardiac death and non-fatal myocardial infarction in patients randomised to thrombectomy
TASTE 2013	7244	Randomised	All-cause mortality at 30 days	No reduction in all-cause mortality in patients randomised to thrombectomy
TOTAL 2015	10 732	Randomised	Death from cardiovascular causes, recurrent myocardial infarction, cardiogenic shock or New York Heart Association class IV heart failure within 180 days	No reduction in cardiovascular events in patients randomised to thrombectomy; stroke events within 30 days higher in patients receiving thrombectomy
Elgendy <i>et al</i> 2015	20 960	Meta-analysis	Mortality, reinfarction and stent thrombosis	No reduction in cardiovascular events in patients randomised to thrombectomy; non-significant increase in the risk of stroke in patients receiving thrombectomy

STEMI, ST-segment elevation myocardial infarction; TAPAS, Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study; TASTE, Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia; TOTAL, Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI.

der nisu dokazali smanjenje kardiovaskularnih događaja kod skupine pacijenata randomiziranih na rutinsku trombektomiju. Učestalost moždanog udara, posebice ishemijskog, bila je veća u pacijenata podvrgnutih trombektomiji<sup>37</sup> (tablica 2). Stoga trenutačno autori ne podupiru rutinsku primjenu trombektomije tijekom primarne PCI kod STEMI-ja, a mnogi istraživači tvrde da trombektomiju treba isključivo primjenjivati samo u bolesnika s velikim trombotskim opterećenjem.<sup>38</sup> U skladu sa spomenutim studijama, tijekom 2015. obnovljene, američke smjernice za primarnu PCI-ja u STEMI-ju snizile su razinu dokaza za rutinsku aspiracijsku trombektomiju s klase IIa u klasu III. (bez dobiti).<sup>39</sup>

### BIORESORPTIVNI STENTOVI

Najnovija vrsta koronarnih stentova jesu bioresorptivni stentovi (BVS) čiji je učinak također ispitan u bolesnika sa STEMI-jem. Diletti *i sur.*<sup>40</sup> proveli su jednu od prvih pilot-studija s BVS-om u 49 pacijenata sa STEMI-jem te su pratili visok uspjeh postupka, izvrsnu apoziciju stenta na optičkoj koherentnoj tomografiji, a nije zabilježena nijedna neuspjela intervencija na ciljnoj leziji unutar 30 dana. Kocka *i sur.*<sup>41</sup> analizirali su 141 bolesnika podvrgnutih primarnoj PCI zbog STEMI-ja i utvrdili visok proceduralni uspjeh i podjednak period bez ponovljenog događaja u usporedbi s bolesnicima koji su dobili metalni stent.

### PERKUTANA KORONARNA INTERVENCIJA NA VIŠE ŽILA

Prema postojećim smjernicama za kliničku praksu, intervenciju na više žila ne treba raditi pri revaskularizaciji arterije odgovorne za infarkt u bolesnika sa STEMI-jem.<sup>39,42</sup> U nedavno dovršenim ispitivanjima PRAMI, CVLPRIT i DANAMI-3-PRIMULTI uočeno je smanjenje kardiovaskularnih događaja (prije svega u smislu manjega broja ponovljenih revaskularizacijskih postupaka) u bolesnika podvrgnutih potpunoj revaskularizaciji tijekom prvotnog događaja<sup>43-45</sup> (tablica 3). Kowalewski *i sur.*<sup>46</sup> proveli su metaanalizu koja je uključivala sedam randomiziranih kontroliranih ispitivanja s 1303 pacijenta te su također pronašli smanjenje u velikim nepovoljnim kardiovaskularnim događajima te ponovljenim infarktima miokarda i postupcima revaskularizacije u bolesnika koji su bili podvrgnuti višezilnoj PCI u usporedbi s onima koji su bili podvrgnuti PCI samo na arteriji odgovornoj

current body of literature does not support the routine use of thrombectomy during primary PCI for STEMI and many investigators argue that thrombectomy should be reserved for those with extensive (large) thrombus burden.<sup>38</sup> The 2015 ACC/AHA/SCAI Focused Update on Primary PCI for STEMI downgraded routine aspiration thrombectomy from Class IIa to Class III (no benefit).<sup>39</sup>

### BIORESORBABLE VASCULAR SCAFFOLDS

The newest iteration of coronary stents, bioresorbable vascular scaffolds (BVS), has also been evaluated in patients with STEMI. Diletti *et al.*<sup>40</sup> completed one of the initial pilot studies with BVS in 49 patients with STEMI and found high procedural success, excellent stent apposition by optimal coherence tomography and no episodes of target-lesion failure to 30 days. Kocka *et al.*<sup>41</sup> evaluated 141 patients undergoing primary PCI for STEMI and found high procedural success and similar event-free survival compared with patients receiving bare metal stents.

### MULTIVESSEL PCI

Current practice guidelines caution against the use of multivessel PCI at the time of infarct-related artery (IRA) revascularisation for patients with STEMI.<sup>39-42</sup> The recently completed Preventive Angioplasty in Acute Myocardial Infarction (PRAMI), Complete versus Lesion-only Primary PCI (CVLPRIT) and Third DANish Study of Optimal Acute Treatment of Patient with ST-segment Elevation Myocardial Infarction: Conventional Primary Angioplasty and Complete Revascularisation versus Treatment of Culprit Lesion only (DANAMI-3-PRIMULTI) trials all found a reduction in cardiovascular events (mainly from fewer repeat revascularisation procedures) for patients undergoing complete revascularisation during the index event<sup>43-45</sup> (Table 3). A meta-analysis by Kowalewski *et al.*<sup>46</sup> that included seven randomised controlled trials with 1303 patients also found a reduction in major adverse cardiovascular events, recurrent MI and repeat revascularisation for patients receiving multivessel PCI compared with those receiving IRA-only PCI. These clinical studies prompted the 2015 ACC/AHA/SCAI Focused Update on Primary PCI for STEMI to change multivessel PCI during STEMI from Class III to Class IIb.<sup>39</sup> The ongoing Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Primary PCI for STEMI (COMPLETE) study with 3900

**TABLE 3. Summary of clinical trials evaluating multivessel percutaneous coronary intervention versus staged percutaneous coronary intervention for patients with ST elevation myocardial infarction and multivessel coronary artery disease.**

Study name/author year	n	Study design	Primary endpoint	Findings
PRAMI 2103	465	Randomised	Death, non-fatal myocardial infarction or refractory angina	Multivessel percutaneous coronary intervention reduced the composite primary endpoint
CVLPRIT 2015	296	Randomised	Death, recurrent myocardial infarction, heart failure and ischaemia-driven revascularisation	Multivessel percutaneous coronary intervention reduced the composite primary endpoint
DANAMI-3-PRIMULTI 2015	627	Randomised	Death, non-fatal reinfarction, ischaemia-driven revascularisation	Multivessel percutaneous coronary intervention reduced the composite primary endpoint; main benefit with fewer repeat revascularisation procedures
Kowalewski <i>et al.</i> 2015	1303	Meta-analysis	Death, recurrent myocardial infarction and repeat revascularisation	Multivessel percutaneous coronary intervention associated with reduction in recurrent myocardial infarction and repeat revascularisation

CVLPRIT, Complete versus Lesion-only Primary PCI; DANAMI-3-PRIMULTI, Third DANish Study of Optimal Acute Treatment of Patient with ST-segment Elevation Myocardial Infarction; PRAMI, Preventive Angioplasty in Acute Myocardial Infarction.

za infarkt. Te su kliničke studije bile poticaj da se u novom izdanju američkih smjernica za primarnu PCI kod STEMI-ja promijeni razina dokaza za PCI na više žila tijekom STEMI-ja iz klase III. u klasu IIb.<sup>39</sup> Studija COMPLETE koja je u tijeku s uključenih 3900 pacijenata koji imaju STEMI vjerojatno će dati konačni odgovor na pitanje primjene potpune revaskularizacije pri primjeni PCI-ja na arteriju odgovornu za infarkt spram konzervativnijeg liječenja (jedina trenutačno dostupna referenca nalazi se na poveznici <http://clinicaltrials.gov/ct2/show/NCT01740479>).

Pacijenti s kardiogenim šokom visokorizična su podskupina pacijenata sa STEMI-jem i višezilnom KBS. Park *et al*<sup>47</sup> analizirali su oko 16 000 pacijenata u korejskom prospektivnom državnom registru kako bi utvrdili je li primjena višezilne PCI povezana s pozitivnim učinkom na smrtnost, u usporedbi s PCI samo na arteriji odgovornoj za infarkt. Nakon korekcije za pridružene čimbenike, pokazalo se da je primjena višezilne PCI povezana s nižom stopom smrti od svih uzroka i u bolnici i pri dugoročnom praćenju.

### SMANJIVANJE VELIČINE INFARKTA

Brza i djelotvorna uspostava epikardijalnog koronarnog toka cilj je primarne PCI i glavna odrednica ishoda u pacijenata sa STEMI-jem. Unatoč kontinuiranom napretku u liječenju pacijenata sa STEMI-jem uporabom radijalnog pristupa, snažnih antitrombotičkih lijekova i integriranih i učinkovitih strategija zbrinjavanja, u znatnog broja bolesnika koji prežive akutni događaj zaostaje određeni stupanj disfunkcije miokarda te su stoga pod većim rizikom od iznenadne srčane smrti.<sup>48</sup> Zbog toga su strategije usmjerene na smanjenja veličine infarkta i dalje predmet aktivnog istraživanja.<sup>49</sup> Mehaničke metode poboljšanja perfuzije koronarnih arterija i smanjivanja tlačnog opterećenja uporabom intraaortalne balonske pumpe nisu se pokazale učinkovite.<sup>50</sup> S druge strane, pokazano je da liječenje supersaturacijom kisikom smanjuje proizvodnju slobodnih radikala i stvara pozitivne promjene upalnog odgovora tijekom akutnog infarkta miokarda.<sup>51</sup> Istraživanje AMIHOT-II pronašlo je pozitivan učinak supersaturacije kisikom u bolesnika s prethodnim STEMI-jem u kojih je primijećeno statistički značajno smanjenje veličine infarkta.<sup>52</sup> Indukcija blage hipotermije raznim uređajima nije dokazala postojanu dobit, prema nekolicini manjih pilot-studija.<sup>53,54</sup> S obzirom na pozitivne učinke hipotermije u širokom rasponu kliničkih situacija, primjerice pri izvanbolničkom zastoju srca te tijekom operacije aortokoronarnog premoštenja, došlo je do porasta interesa za njezinu primjenu prije ili tijekom postupka primarne PCI u bolesnika sa STEMI-jem.<sup>55</sup> Studija CHILL-MI nije dokazala smanjenje veličine infarkta u pacijenata randomiziranih u skupinu podvrgnutu endovaskularnom hlađenju.<sup>56</sup> Ipak, ako se zbroje podatci iz studije CHILL-MI i inicijalne studije sigurnosti RAPID MI-ICE, čini se da hipotermija ipak dovodi do relativnog smanjenja veličine infarkta od oko 15%; u pacijenata s prednjim STEMI-jem primijećen je još veći pozitivan učinak.<sup>57</sup>

### NESTABILNA ANGINA / INFARKT MIOKARDA BEZ ELEVACIJE ST SEGMENTA

Pacijenti s nestabilnom anginom i infarktom miokarda bez elevacije ST segmenta (NSTEMI) heterogena su kohorta s

patients with STEMI will likely yield the definite answer on the issue of complete revascularisation at the time of IRA PCI versus conservative therapy (only reference available at this time is from <http://clinicaltrials.gov/ct2/show/NCT01740479>). A high-risk subgroup of patients with STEMI and multivessel CAD are those with cardiogenic shock. Park *et al*<sup>47</sup> evaluated approximately 16 000 patients participating in a nationwide, prospective registry in Korea to study whether multivessel PCI versus IRA-only PCI was associated with a mortality benefit. After adjusting for confounding factors, multivessel PCI was associated with lower all-cause death both in-hospital and at long-term follow-up, compared with IRA-only PCI.

### REDUCTION IN INFARCTION SIZE

Prompt and effective restoration of epicardial coronary flow is the goal of primary PCI and the main determinant of outcome in patients with STEMI. Despite continued advances in the care of patients with STEMI with the use of radial artery access, potent antiplatelet agents and integrated and efficient systems of care, a significant number of patients surviving the acute event experience some degree of myocardial dysfunction and are therefore at increased risk for sudden cardiac death.<sup>48</sup> Strategies directly targeted to limit infarct size have thus been an area of active research.<sup>49</sup> Mechanical methods to augment coronary artery perfusion and reduce afterload with intra-aortic balloon counterpulsation have not shown benefit.<sup>50</sup> The use of supersaturated oxygen therapy has been shown to reduce free radical production and favourably alter components of the inflammatory response during an acute myocardial infarction.<sup>51</sup> The Acute Myocardial Infarction with Hyperoxemic Therapy (AMIHOT-II) trial recently reported a benefit of supersaturated oxygen for patients with an anterior STEMI with a statistically significant reduction in infarct size.<sup>52</sup> Induction of mild hypothermia with various devices in small pilot studies failed to show a consistent benefit.<sup>53,54</sup> Hypothermia has been used in a variety of clinical settings including out-of-hospital cardiac arrest and during cardiopulmonary bypass; given the benefits seen, interest has grown to use hypothermia either before or during primary PCI for STEMI.<sup>55</sup> The large-scale Rapid Endovascular Catheter Core Cooling Combined With Cold Saline as an Adjunct to Percutaneous Coronary Intervention for the Treatment of Acute Myocardial Infarction (CHILL-MI) study did not show a reduction in infarct size in those patients randomised to endovascular cooling.<sup>56</sup> However, combining patients from CHILL-MI and an initial safety study called Rapid Intra-vascular Cooling in Myocardial Infarction as Adjunctive to Percutaneous Coronary Intervention (RAPID MI-ICE), there did appear to be benefit for hypothermia with a relative reduction in infarct size of approximately 15%; patients with an anterior STEMI derived even greater benefit.<sup>57</sup>

### UNSTABLE ANGINA/NON-STEMI

Patients with unstable angina and non-STEMI (NSTEMI) represent a heterogeneous cohort with variable risks for recurrent MI and death.<sup>58</sup> A number of risk scores including Global Registry of Acute Coronary Events (GRACE), TIMI and history, electrocardiogram, age, risk factors, troponin (HEART) and biomarkers have thus been developed to objectively assess



različitim rizikom od ponovljenog infarkta miokarda i smrti.<sup>58</sup> Stoga je razvijeno više biomarkera te bodovnih sustava rizika, uključujući GRACE, TIMI i HEART kako bi se moglo objektivno procijeniti rizike u tih pacijenata te odrediti najbolji način za daljnju dijagnostiku i primjenu invazivnog ili medikamentnog liječenja.<sup>59-63</sup> Bolesnici pristigli u hitnu službu sa sumnjom na angiozni bol vrlo su česti te čine oko 10 % ukupnoga broja primljenih pacijenata, no još je uvijek velik izazov točno odrediti koji pacijenti imaju nizak i vrlo nizak rizik od budućih kardiovaskularnih događaja te su prikladni kandidati za rani otpust, čime se izbjegava bolničko liječenje. Carlton *i sur.*<sup>64</sup> analizirali su uporabu ubrzanog dijagnostičkog protokola temeljenog na jednom visoko osjetljivom troponinu T koji se određivao pri primitku u bolnicu te modificiranom zbroju prema Goldmanovoj ljestvici za određivanje rizika. U kohorti od 960 pacijenata ubrzani dijagnostički protokol identificirao je da je u oko 40 % pacijenata primjeren rani otpust, pri čemu je samo jedan pacijent (0,3 %) unutar 30 dana doživio nesmrtonosan infarkt miokarda.

### TERAPIJA HIPOLIPEMICIMA

Ranije studije koja su istraživale nestatinski lijek ezetimib dokazale su dramatično smanjenje vrijednosti LDL kolesterola (LDL), no nisu registrirale pozitivne učinke na posredne biljege ateroskleroze, uključujući debljinu intime-medije stijenke karotidnih arterija.<sup>65</sup> S druge strane, nedavno objavljeno istraživanje IMPROVE-IT koje je uključivalo više od 18 000 pacijenata s akutnim koronarnim sindromom te otkrilo znatno smanjenje kombiniranih ciljnih ishoda koji su se sastojali od kardiovaskularne smrti, nesmrtonosnog infarkta miokarda, nestabilne angine zbog koje je nužna hospitalizacija, koronarne revascularizacije i nesmrtonosnog moždanog udara u bolesnika koji su dobivali kombiniranu terapiju sa simvastatinom i ezetimibom.<sup>66</sup> Ovo je istraživanje vrlo važno jer je bilo prvo istraživanje koje je upozorilo na dodatnu kliničku korist od dodavanja nestatinskog lijeka uz standardnu terapiju statinima. U nizu kliničkih ispitivanja uporabom intravaskularnog ultrazvuka (IVUS) dokazano je da intenzivna terapija statinima uzrokuje stabilizaciju ili smanjivanje koronarnog plaka.<sup>67,68</sup> U studiji PRECISE-IVUS dobiveni su slični rezultati kombinacijom atorvastatina i ezetimiba: kombinirana terapija bila je povezana s nižom razinom LDL kolesterola i većom regresijom koronarnog plaka u usporedbi s monoterapijom atorvastatinom.<sup>69</sup> U usporedbi s gore navedenim studijama u kojima su primjenjivani IVUS i različiti statini kako bi se postiglo smanjivanje plaka, kombinirana terapija atorvastatinom i ezetimibom postigla je najznačajnije dosad utvrđeno smanjivanje plaka (smanjenje volumena plaka ateroma od 2,3 %).

### ANTITROMBOCITNA TERAPIJA

Usprkos velikom iskustvu u liječenju s klopidoogrelom, lijekom iz druge generacije tienopiridina, prisutnost ograničenja zbog biorapoloživosti, početka djelovanja i djelotvornosti potaknuli su razvoj nove generacija lijekova, prasugrela i tikagrelora.<sup>70,71</sup> Prema rezultatima studija, čini se da je učestalost uporabe tih lijekova u svakodnevnoj praksi oko 30 %, iako postoje regionalne i nacionalne razlike.<sup>11</sup> U istraživanju TRITON-TIMI<sup>38</sup> prasugrel se pokazao povezanim s velikim krvarenjem u bolesnika s prethodnim prolaznim ishemijskom događajem ili

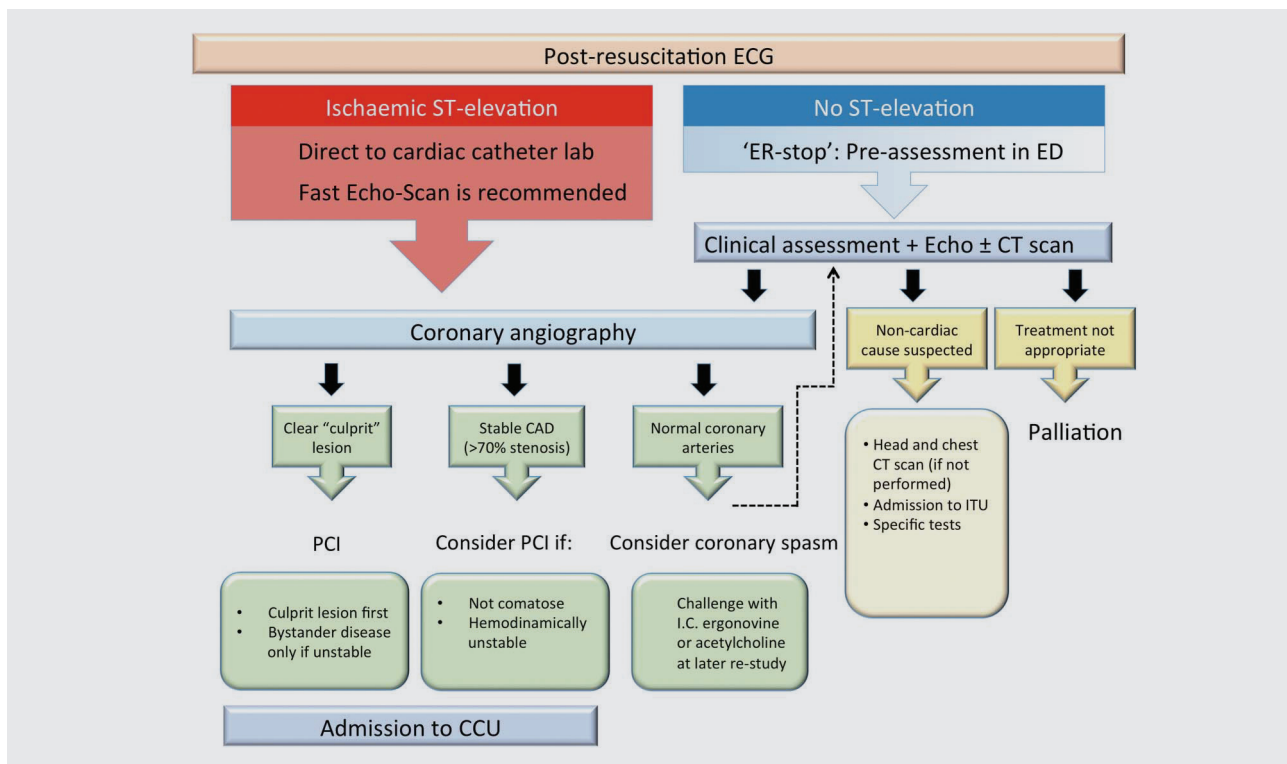
these risks to determine best practices for diagnostic testing and use of invasive and medical therapy.<sup>59-63</sup> Patients presenting to the emergency department with presumed cardiac chest pain are common, accounting for approximately 10% of patients evaluated. The ability to identify patients with a low and very low risk for future cardiovascular events who are appropriate candidates for early discharge thus avoiding hospital admission remains challenging. Carlton *et al.*<sup>64</sup> evaluated the use of an accelerated diagnostic protocol using a single high-sensitivity troponin T that was drawn at hospital presentation and the modified Goldman risk score. Among the cohort of 960 patients, the accelerated diagnostic protocol identified approximately 40% that were suitable for early discharge with only one patient (0.3%) experiencing a non-fatal MI within 30 days.

### LIPID-LOWERING THERAPY

Previous studies evaluating the non-statin drug ezetimibe found dramatic reductions in low-density lipoprotein (LDL) cholesterol levels, but failed to show any benefit on surrogate markers of atherosclerosis, including carotid-artery intima-media thickness.<sup>65</sup> In contrast, the recently reported Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) enrolled over 18 000 patients with an acute coronary syndrome and found a significant reduction in the combined cardiovascular endpoints of cardiovascular death, non-fatal myocardial infarction, unstable angina requiring hospitalisation, coronary revascularisation and non-fatal stroke in those receiving combination therapy with simvastatin and ezetimibe.<sup>66</sup> This trial is highly relevant as it was the first to show an incremental clinical benefit of adding a non-statin agent to standard statin therapy. Using intravascular ultrasound (IVUS) imaging, intensive statin therapy has been shown in multiple clinical trials to cause coronary plaque stabilisation and/or plaque regression.<sup>67,68</sup> The Plaque Regression With Cholesterol Absorption Inhibitor or Synthesis Inhibitor Evaluated by Intravascular Ultrasound (PRECISE-IVUS) study found similar findings with combined atorvastatin and ezetimibe; that is, combination therapy was associated with lower levels of LDL cholesterol and greater coronary plaque regression, compared with monotherapy with atorvastatin alone.<sup>69</sup> In comparison with the aforementioned studies using IVUS and various statins to assess for plaque regression, combination therapy with atorvastatin and ezetimibe achieved the most significant plaque regression seen to date (2.3% reduction in plaque atheroma volume).

### ANTIPLATELET THERAPY

Despite extensive experience with the second-generation thienopyridine clopidogrel, limitations in bioavailability, onset of action and efficacy spurred the development of the newer generation agents, prasugrel and ticagrelor.<sup>70,71</sup> Studies suggest that use of these agents in contemporary practice is approximately 30%, although regional and national variations exist.<sup>11</sup> In the TRial to Assess Improvement in Therapeutic Outcomes by Optimising Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) prasugrel was associated with excessive-bleeding events in patients with a prior transient ischaemic accident or stroke,



**FIGURE 4. Proposed treatment algorithm based upon the postresuscitation electrocardiogram (ECG) in patients with out-of-hospital cardiac arrest. Figure 2 from Nerla et al.<sup>73</sup> CCU, coronary care unit; CT, computed tomography; ED, emergency department; ER, emergency room; ITU, intensive care unit.**

moždanim udarom, u pacijenata starijih od 75 godina te u pacijenata s tjelesnom težinom < 60 kg.<sup>72</sup> Podatci o krvarenju uz prasugrel u usporedbi s klopidogrelom ograničeni su na one iz randomiziranih kliničkih ispitivanja. Klingenberg *i sur.*<sup>73</sup> analizirali su sklonost krvarenju u 2286 pacijenata s akutnim koronarnim sindromom ovisno o primjeni klopidogrela i prasugrela. Pacijentima s povećanim rizikom od krvarenja dana je doza od 5 mg prasugrela. Nakon godine dana učestalost je krvarenja bila slična za oba lijeka, a autori su naglasili da studija nije bila namijenjena istraživanju djelotvornosti. Tikagrelor je bio prvi antitrombotični lijek za koji je dokazano da smanjuje smrtnost nakon jedne godine u pacijenata s akutnim koronarnim sindromom, u ispitivanju PLATO.<sup>74</sup> U detaljnoj analizi svih uzroka vaskularnih i ostalih smrtnih događaja u PLATO ispitivanju koju su proveli Varenhorst *i sur.*<sup>75</sup> zaključili su da pozitivan učinak tikagrelora na smrtnost proizlazi iz smanjenja učestalosti iznenadne srčane smrti. Mehanizam kojim do toga dolazi i dalje je nerazjašnjen, no smatra se da je povezan s potencijalnim pleiotrofnim učincima tikagrelora.

## Izvanbolnički srčani zastoj

Nedavno objavljene smjernice preporučaju da se u pacijenta koji su doživjeli izvanbolnički srčani zastoj razmotri hitna koronarografija.<sup>33,76</sup> Postupak donošenja odluke o provođenju hitne koronarografije relativno je jednostavan u bolesnika s ritmom koji je zahtijevao defibrilaciju, bolesnika s kratkim vremenom između zastoja srca i provođenja oživljavanja te u onih s elevacijom ST segmenta na elektrokardiogramu nakon oživljavanja (slika 4). Odluka o postupku postaje zahtjevnija

those older than 75 years and those with body weight <60 kg.<sup>72</sup> Data regarding bleeding events with prasugrel compared with clopidogrel outside of randomised trials is limited. Klingenberg et al<sup>73</sup> evaluated 2286 patients with acute coronary syndromes, applied propensity score methodology and compared bleeding events between those receiving clopidogrel and prasugrel. For patients at increased risks for bleeding, the reduced maintenance dose of 5 mg of prasugrel was studied. At 1 year, bleeding events were similar between the two agents; that authors noted that the study was not designed to compare efficacy. Ticagrelor was the first antiplatelet agent to demonstrate a reduction in 1-year mortality in patients with ACS in the PLATelet inhibition and patients Outcome (PLATO) trial.<sup>74</sup> In a detailed evaluation of all causes of vascular and overall death events in the PLATO trial, Varenhorst et al<sup>75</sup> found the mortality benefit of ticagrelor was mediated by a reduction in sudden death events. The mechanism for this remains unclear but is thought to be related to potential pleiotropic effects of ticagrelor.

## Out-of-hospital cardiac arrest

Recent practice guidelines recommend consideration of early coronary angiography in patients with out-of-hospital cardiac arrest.<sup>33,76</sup> The decision to proceed with early angiography is relatively straightforward in patients with an initial shockable rhythm, those with a short time from cardiac arrest to resuscitation and those with ST-segment elevation on the post-resuscitation ECG (Figure 4). Management options become challenging in those without clear ST-segment elevation on

u bolesnika bez jasne elevacije ST segmenta nakon oživljavanja, u onih s inicijalnim ritmom koji ne zahtijeva defibrilaciju te u pacijenata s raznim prediktorima loših neuroloških ishoda, uključujući i poodmaklu dob (> 85 godina), prolongirano kardiopulmonalno oživljavanje, izostanak započinjanja oživljavanja od osoba koje su svjedočile arestu i terminalna bubrežna bolest.<sup>77</sup>

the postresuscitation ECG, those with an initial unshockable rhythm and those with various predictors of poor neurological outcome, including advanced age (>85 years), use of ongoing cardiopulmonary resuscitation, absence of bystander cardiopulmonary resuscitation and end-stage renal disease.<sup>77</sup>

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