Godina 2016. u kardiologiji: akutni koronarni sindrom

The year in cardiology 2016: acute coronary syndromes

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Uvod

U godini 2016. objavljeno je nekoliko studija o patofiziologiji akutnoga koronarnog sindroma (ACS), primjerice o ulozi bazofila i eozinofila u patofiziologiji bolesti. Također se pojavljuju novi zanimljivi podatci o patofiziološkom mehanizmu vrlo kasne tromboze stenta te o ulozi neutrofila u remodeliranju klijetke. Isto tako pojavljuju se nove informacije o ranoj dijagnostici ACS-a s pomoću visokosenzitivnog troponina (hsTn) i o ulozi novih dijagnostičkih biomarkera i novih kliničkih bodovnih sustava za procjenu rizika. Glede antitrombocitne terapije, godina 2016. donijela je nove podatke o trajanju dvojne antitrombocitne terapije (DAPT) i smjernica za liječenje populacije starijih, kakvih je sve više u kliničkoj populaciji. Naposljetku, pojavljuju se novi podatci za različite podskupine bolesnika. Ovaj pregledni rad navedene studije ukratko prikazuje u **Tablici 1**.

Preamble

The year 2016 brought us several studies on the pathophysiology of acute coronary syndrome (ACS), in particular, on the role of basophils and eosinophils in the mechanism of disease. New puzzling data have also emerged on the pathomechanisms of very late stent thrombosis and the role of neutrophils in ventricular remodelling. New information has also been published on the early diagnosis of ACS by high sensitivity troponin (hsTn) and the role of new exciting biomarkers and clinical scores on risk stratification. With regards to antithrombotic treatment, the year 2016 has brought important new data on the duration of dual antiplatelet therapy (DAPT) and on the management of the growing population of very elderly. Finally, new interesting information has been published on the outcome of specific patient subsets. The studies reported in this review are summarized in **Table 1**.

TABLE 1. Summary of the main studies.

Topic	Main messages	References
Mechanisms	Allergic immunity is altered in ACS	Niccoli[1]
	VLST is frequently associated to suboptimal stent implantation	Taniwaki[2]
	In experimental models neutrophil depletion is associated to worse remodelling	Horckmans[3]
Early diagnosis	The best hsTn algorithm to rule out ACS remains controversial	Pickering[5], Shah[4]
	Potential role of micro-RNA	Coskunpinar[7]
	The role of coronary computed tomography angiography in the emergency department in patients with suspected ACS is limited	Dedic[8]
Risk stratification	GDF-15 predicts both bleeding and ischemic risk	Hagstrom[11]
	New clinical risk scores to predict in-hospital mortality and medium-term risk of sudden cardiac death in patients admitted with ACS	Hess[10]
Treatment	The efficacy of Cangrelor compared to clopidogrel previously found in the CHAMPION PHOENIX trial is independent of the puncture site	Gutierrez[13]
	The pharmacodynamic effects of Ticagrelor are impaired by morphine	Kubica[16]
	Data from SWEDEHEART database confirm the better efficacy of Ticagrelor as compared to Clopidogrel in ACS in the real world	Sahlen[17]
	The pharmacodynamic effects of crushed Prasugrel tablets are better than those of intact tablets	Rollini[19]
	A meta-analysis suggests that dual antiplatelet therapy beyond one year after ACS reduces subsequent ischemic events	Udell[20]
	The addition of ezetimibe to simvastatin reduced first and subsequent cardiovascular events in ACS patients in the IMPROVE-IT trial	Murphy[31]
	A sub-study of the LEADERS FREE trial confirms that Biolimus-A9 polymer-free coated stent is superior to bare metal stent in ACS patients with high-bleeding risk on one-month double antiplatelet treatment	Naber[22]
	A real-world analysis fails to show superiority of bivaluridin as compared to other anti-thrombotic treatments	Sirker[28]
	The efficacy of early beta-blockers in STEMI remains controversial	Garcia-Ruiz[29]
	In early STEMI admitted to non-capable PCI centres, transfer for primary PCI is better than fibrinolysis if the delay is less than 140 min	Carrillo[32]
	In NSTEMI a single-staged compared with a multi-staged PCI is associated with a lower rate of target vessel revascularization during follow-up	Sardella[33]
	In the very elderly with ACS, an invasive approach is associated to a better outcome as compared to a conservative approach	Tegn[36]
	PCI in unprotected left main stenosis is associated with comparable clinical outcomes to those observed with coronary artery grafting at long-term follow-up	Pyxaras[34]
	The outcome of left ventricular assist device implanted in patients with ACS is similar to that observed in stable patients	Acharya[38]
Outcomes in specific patient populations	Women: a statement from the American Heart Association on ACS in women summarizes the main differences between men and women in this setting.	Mehta[39]
	Smokers: smoking is independently associated to better left ventricular remodelling	Symons[40]
	Rheumatoid arthritis: among patients with ACS rheumatoid arthritis is associated to a worse outcome	Mantel[41]
	Vasospastic angina: among patients with vasospastic angina those who present with aborted sudden cardiac death have a worse outcome during follow up	Ahn[42]
	Takotsubo syndrome: the outcome of the "happy heart syndrome" is similar to that of the "broken heart syndrome"	Ghadri[44]

ACS, acute coronary syndrome; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; VLST, very late stent thrombosis.

Mehanizmi

PATOFIZIOLOGIJA AKUTNOGA KORONARNOG SINDROMA

Spontani ACS može nastati kao posljedica fisure plaka, erozije plaka ili funkcionalnih promjena epikardijalnih koronarnih arterija ili pak preko vazokonstrikcijske reakcije u mikrocirkulaciji. Aktivacija upalnih stanica temeljni je događaj pri nastanku fisure ili erozije, iako su mehanizmi koji uzrokuju nestabilnost plaka u većem dijelu različiti između navedenih stanja. Dok je aktivacija

Mechanisms

PATHOGENESIS OF ACS

Spontaneous ACS can be caused by plaque fissure, plaque erosion, or functional alterations of epicardial coronary arteries or by vasoconstriction of the microcirculation. Activation of inflammatory cells plays a key role in both plaque fissure and erosion although the mechanisms leading to plaque instability are substantially different in these two conditions. Indeed, while monocyte and lymphocyte activation is the key altera-

monocita i limfocita osnovni mehzanizam razvoja fisure plaka, aktivacija neutrofila osnova je procesa erozije plaka. Uloga aktivacije eozinofila i bazofila još nije do sada potpuno objašnjena. *Niccoli i sur.*[1] pronašli su mnogo viši stupanj aktivacije eozinofila i bazofila s pomoću protočne citomerije u bolesnika s ACS-om nego u bolesnika sa stabilnom anginom pektoris. Nadalje, u prospektivnim kohortnim studijama pronađeno je da su više razine eozinofilnoga kationskog proteina (ECP) bile povezane s težim kliničkim ishodima u razdoblju praćenja. Navedeni podatci impliciraju da bi bi bilo opravdano testirati nove terapijske strategije koje bi ciljale na eozinofile u bolesnika s ACS-a i povišenim razinama ECP-a.

TROMBOZA STENTA

Dobro nam je poznato da vrlo kasna tromboza stenta može biti uzrokom ACS-a. Patofiziološki mehanizmi vrlo kasne tromboze koji slijede nakon ugradnje stenta koji otpušta lijek (DES) nisu potpuno poznati. Primjenom optičke koherentne tomografije (OCT) *Taniwaki i sur.*[2] ispitivali su potencijalne uzroke za neželjene događaje. Pronašli su da su glavni patofiziološki mehanizmi vrlo kasne tromboze stenta prema učestalosti: (**i**) malpozicija stenta, (**ii**) neoateroskleroza, (**iii**) otkrivenost potpornoga sloja, (**iv**) nedovoljna ekspanzija potpornice. Longitudinalna ekstenzija malpozicioniranog stenta i otkrivanje potpornoga sloja bili su u najvažnijoj korelaciji s formacijom tromba. Ove spoznaje mogu proširiti potrebu za kliničkom primjenom OCT-a u optimizaciji implantacije stenta.

REMODELIRANJE

Vrlo važan izazov u ACS-u jesu mehanizmi koji su odgovorni za remodeliraje lijeve klijetke nakon infarkta miokarda (IM). U pretkliničkoj studiji na miševima *Horckmans i sur.*[3] pronašli su da su u miševa s nedostatkom neutrofila češće nastupali pogoršanje srčane funkcije, pojačana fibroza i razvoj progresivnoga srčanog popuštanja. Stoga, dok se povišene vrijednosti neutrofila smatraju prediktorom neželjenih događaja i smrtnosti u bolesnika s ACS-om i njihov doprinos akutnoj upalnoj fazi nakon IM-a dominantno se podrazumijeva negativnim, ove, nove spoznaje upućuju na to da neutrofili sudjeluju u oporavku nakon IM-a tako da transformiraju makrofage prema razrješujućem fenotipu koji izvrsno obavlja funkciju uklanjanja staničnog debrisa. Novootkrivene uloge neutrofila trebale bi se uzimati u obzir pri dizajnu i primjeni potentnih antineutrofilnih lijekova u bolesnika s IM-om.

Rana dijagnostika

TROPONINI

Obrada bolesnika koji se na hitnom prijmu jave zbog sumnje na ACS ostaje predmetom i dalje prisutnih kliničkih izazova. Tradicionalna procjena rizika uključivala je kliničku procjenu rizika na temelju simptoma, čimbenika kardiovaskularnog rizika, serijskim snimanjem 12-kanalnog EKG-a i mjerenjima hsTn, nakon čega su obično slijedile dodatne kardiološke dijagnostike, bilo ambulatno bilo hospitalno. U nekoliko je kohortnih studija pokazano da bolesnici s nemjerljivim vrijednostima hsTn u plazmi imaju niski rizika za razvoj IM-a. No, optimalni pristup i precizne granične vrijednosti hsTn kojima bi odmah bilo procijenjeno koji bi se bolesnici mogli otpustiti bez dodatnih rizika predmet su daljnjih rasprava. *Shah i sur.*[4] ispitivali su vrijednosti hsTnI u prospektivnoj kohortnoj studiji na 6304 uzastopno uključena bolesnika sa sumnjom na AKS u hitnom prijmu, provedenoj u 4 sekundarna i tercijarna hospitalna centra u Škotskoj. Ispitivane su vrijednosti hsTnI kod kliničke prezentacije

tion in plaque fissure, neutrophil activation is a crucial player in plaque erosion. The role of eosinophil and basophil activation is still largely unknown. Niccoli *et al.*[1] found a higher degree of both eosinophil and basophil activation, as assessed by flow cytometry, in patients with ACS than in those with stable angina. Furthermore, in a prospective cohort study they found that higher levels of eosinophil cationic protein (ECP) were associated with a worse outcome during follow-up. This suggests that novel therapies targeting eosinophils should be tested in ACS patients exhibiting raised ECP levels.

STENT THROMBOSIS

It is well known that very late stent thrombosis is a possible cause of ACS. The pathomechanisms underlying very late stent thrombosis after implantation of drug-eluting stents (DES) are incompletely understood. Using optical coherence tomography (OCT), Taniwaki *et al.*[2] investigated potential causes of this adverse event. They found that the leading associated findings in very late stent thrombosis were in descending order: (**i**) stent malapposition, (**ii**) neoatherosclerosis, (**iii**) uncovered stent struts, and (**iv**) stent underexpansion. The longitudinal extension of malapposed and uncovered struts was the most important correlate of thrombus formation. These findings might further expand the clinical utilization of OCT in optimizing the results of stent implantation.

REMODELLING

Another important issue in ACS are the mechanisms responsible for left ventricular remodelling after myocardial infarction (MI). In an elegant experimental study in a mice model of MI, Horckmans *et al.*[3] found that neutrophil-depleted animals had worsened cardiac function, increased fibrosis, and progressively developed heart failure. Thus, while high neutrophil counts are considered as predictor of adverse clinical outcomes and mortality in patients with ACS and their contribution in the acute inflammatory phase after MI is generally considered detrimental, these data suggest that neutrophils participate in MI repair skewing macrophages towards a resolving phenotype, which mediates efficient clearance of cell debris. This novel role for neutrophils should be taken in account when designing and applying 'aggressive' anti-neutrophil treatments in the setting of MI.

Early diagnosis

TROPONINS

The evaluation of patients presenting at the emergency department (ED) with suspected ACS remains a clinical challenge. The traditional assessment includes clinical risk assessment based on symptoms, cardiovascular (CV) risk factors with serial electrocardiograms and hsTn measurements, often followed by advanced cardiac testing as inpatients or outpatients. With regards to hsTn, several cohort studies have shown that patients with undetectable plasma hsTn concentrations at presentation are at low risk of MI. However, the optimal approach and threshold of hsTn for the identification of low-risk patients suitable for immediate discharge is still debated. Shah *et al.*[4] did a prospective cohort study of 6304 consecutively enrolled patients with suspected ACS presenting to 4 secondary and tertiary care hospitals in Scotland. They measured plasma Tn concentrations at presentation us-

i procijenjena je negativna prediktivna vrijednost raspona hsTnI za primarni neželjeni ishod (IM, kasni IM ili smrt tijekom razdoblja od 30 dana). Medijan vremena dolaska u hitan prijam bio je 54 minute. Pronađeno je da su koncentracije hsTn manje od 5ng/L pri dolasku značile njihovu negativnu prediktivnu vrijednsost do iznosa od barem 99,5 %. S takvim, graničnim vrijednostima dvije trećine bolesnika sa sumnjom na ACS mogle bi biti otpuštene uz vrlo nisku očekivanu stopu neželjenih događaja. Kada bi se klinički primjenjivale navedene granične vrijednosti, mogao bi se dvostruko povećati broj izravno otpuštenih bolesnika primljenih radi obrade u hitnom prijmu.

Pickering i sur.[5] ispitivali su protokol 0 – 1 sat za isključenje, predložen u trenutačnim smjernicama Europskoga kardiološkog društva (ESC) za zbrinjavanje ACS-a u bolesnika bez ST elevacije kod 2222 bolesnika sa serijskim mjerenjima hsTnT i hsTnI. Primjena hsTnT u 0-1 algoritmu isključila je 1425 bolesnika (64,1 %), uz senzivitvnost od 97,1 %, dok je 0-1 hsTnI u algoritmu 0-1 isključio 1205 bolesnika (54,2%) uz senzitivnost od 98,8 %. Zaključeno je da algoritam ESC o 0 – 1 sat za isključivanje akutnog IM-a kod blago povišenih vrijednosti troponina može biti nedovoljan za liječnike na hitnom prijmu kako bi bolesnika sigurno mogli otpustiti kući. Tako da procjena optimalnog algoritma hsTn za isključenje, ali i kriterija za prijam zbog ACS-a u okrilju hitnog prijma ostaje predmet daljnjih rasprava.[6] Također primjena dodatnih biljega poput kopeptina ostaje kontroverznom.

Iz sfere novih biomarkera, u studiji koja je testirala učinkovitost u ranoj dijagnostici ACS-a, *Coskupinar i sur.*[7] ispitivali su dijagnostički potencijal cirkulacijskih mikro-RNA. Pronašli su da je miR-221-3p bio u bitnoj pozitivnoj korelaciji s razinama Tn, GRACE i SYNTAX bodovnim sustavima, odnosno u negativnoj korelaciji s postinfarktnim sistoličkom funkcijom lijeve klijetke. Autori su zaključili da miR-221-3p nudi obećavajući potencijal u dijagnostici ACS-a.

KORONARNA ANGIOGRAFIJA S POMOĆU KOMPJUTORIZIRANE TOMOGRAFIJE

Nemamo sigurnih spoznaja ima li dijagnostički pristup koji uključuje ranu MSCT koronarografiju (CCTA) prednosti s obzirom na trenutačni standard optimalnoga zbrinjavanja u hitnom prijmu, koji uključuje hsTn za bolesnike sa sumnjom na ACS. U prospektivnu multicentričnu randomiziranu studiji *Dedic i sur.*[8] uključili su 500 bolesnika sa simptomima koji upućuju na ACS u hitnim prijmovima 5 općih i 2 kliničke bolnice u Nizozemskoj. Primarni je ishod uključivao broj bolesnika sa znatnom koronarnom bolesti srca, koji bi trebali revaskularizaciju unutar 30 dana. Nije bilo razlike u primarnom ishodu. Otpust s hitnog prijma nije bio mnogo učestaliji u skupini koja je učinila CCTA, a i vremena su boravka bila podjednaka. Autori su zaključili da u slučaju dostupnosti hsTn-a u hitnom prijmu, CCTA ne nudi znatnije prednosti pri identifikaciji većega broja bolesnika sa znatnom koronarnom bolesti srca, koji bi zahtijevali koronarnu revaskularizaciju, niti da skraćuje trajanje boravka u bolnici te ne dopušta izravan otpust.

Stratifikacija rizika

KLINIČKI BODOVNI SUSTAVI

McNamara i sur.[9] analizirali su podatke iz registra *ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry – GWTG (Get With the Guidelines)* te su razvili multivarijatni hijerarhijski model logističke regresije koji je procjenjivao učestalost intrahospitalne smrtnosti. Ispitiavana

ing a hsTnI assay and evaluated the negative predictive value of a range of hsTnI concentrations for the primary outcome of index MI, or subsequent MI or cardiac death at 30 days in derivation and validation cohorts. The median time from arrival in the ED to blood sampling for measurement of hsTn was 54 min. They found that a hsTn concentration of less than 5 ng/L at presentation met their pre-specified criteria for a negative predictive value of at least 99.5%. At this threshold, almost two-thirds of patients with suspected ACS could have been discharged with very few cardiac events. Indeed, implementation of this threshold could double the number of patients discharged directly from the ED.

In one study, Pickering *et al.*[5] tested the 0–1 h rule out algorithm proposed by the current European Guidelines on 2015 ESC guidelines for the management of ACS in patients presenting without persistent ST-segment elevation, in 2222 patients with serial hsTnT and hsTnI measurements. The 0-1 h hsTnT algorithm ruled out 1425 patients (64.1%) with a sensitivity of 97.1%. The 0–1 h hsTnI algorithm ruled out 1205 patients (54.2%) with a sensitivity of 98.8%. They concluded that the sensitivity of the European Society of Cardiology rapid assessment 0-1 h algorithm to rule-out AMI with high-sensitivity troponin may be insufficient for some ED physicians to confidently send patients home. Thus, the identification of the optimal rule-out hsTn algorithm in patients with suspected ACS admitted to ED remains debated as well as the optimal rule-in algorithm.[6] Also controversial is the utilization of a second biomarker like copeptin.

With regards to new biomarkers in the early diagnosis of ACS, in a proof of concept study Coskunpinar *et al.*[7] assessed the potential diagnostic role of circulating micro-RNAs in patients with ACS. They found that miR-221-3p was significantly positively correlated with Tn levels, GRACE and SYNTAX Score and inversely correlated with post-MI left ventricular systolic function. They conclude that miR-221-3p may be a promising biomarker for early diagnosing of ACS.

CORONARY COMPUTED TOMOGRAPHY ANGIOGRAPHY

It is uncertain whether a diagnostic strategy supplemented by early coronary computed tomography angiography (CCTA) is superior to contemporary standard optimal care including hsTn for patients suspected of ACS in the ED. In a prospective, open-label, multicentre, randomized trial, Dedic *et al.*[8] enrolled 500 patients presenting with symptoms suggestive of an ACS at the ED of 5 community and 2 university hospitals in the Netherlands. The primary endpoint was the number of patients identified with significant coronary artery disease requiring revascularization within 30 days. There was no difference in the primary endpoint. Discharge from the ED was not more frequent after CCTA and length of stay was similar. The authors conclude that in the era of hsTns, CCTA does not identify more patients with significant CAD requiring coronary revascularization, neither does it shorten hospital stay, or allow for more direct discharge from the ED.

Risk stratification

CLINICAL SCORES

McNamara *et al.*[9] using the ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry–GWTG (Get With

populacija (243 440 bolesnika iz 655 bolnica) bila je podijeljena na 60 %-tni uzorak za derivaciju modela, a preostalih 40 % činilo je model za ispitivanje validacije. Stvoren je simplificirani sustav procjene rizika, koji bi omogućivao prospektivnu procjenu rizika u kliničkom zbrinjavanju. Dob, frekvencija srca, sistolički tlak, prezentacija nakon aresta srca, prezentacija s popuštanjem srca, prezentacija s akutnim infraktom miokarda sa ST elevacijom, klirens kreatinina i omjer Tn svi su bili neovisno povezani s intrahospitalnom smrtnošću. Stope smrtnosti pokazale su varijacije prema grupama rizika, u rasponu od 0,4 % u najnižoj grupi rizika (zbroj bodova <30) do 49,5% u grupi s najvišim rizikom (zbroj bodova >59). Rad je dopunio spoznaje stvorene na učestalosti smrtnosti za bolesnike s akutnim IM-om. Premda ima vrijednost za selekcioniranu populaciju u trenutku njihova razvoja, promjene u profilu bolesnika i terapijskom zbrinjavaju AKS-a zahtijevaju dodatno obnavljanje podataka i proračuna, što može biti predmet novih bodovnih sustava procjene.

U grupiranoj kohortnoj studiji koja je uključivala individualne podatke od 48 286 bolesnika iz četiriju studija, *Hess i sur.*[10] pronašli su da je iznenadna srčana smrt (SCD) odgovorna za trećinu ukupne kardiovaskularne smrtnosti, tijekom jednogodišnjeg praćenja, i da su smanjena sistolička funkcija lijeve klijetke, starija dob, šećerna bolest, niža bubrežna funkcija, viša frekvencija srca, prethodni infarkt, periferna arterijska bolest, azijska rasa, muški spol i visok stupanj prema klasifikaciju po Killipu bili znatno povezani sa SCD-om. Također su izveli bodovni sustav iz dobivenih podataka, koji je mogao procijeniti rizik od SCD-a u rasponu 0,1 – 56,7 %. Taj bodovni sustav mogao bi uz prosjenu sistoličke funkcije pomoći u identifikaciji kandidata za ugradnju kardioverterskih defibrilatora, iako su potrebne dodatne studije prospektivne procjene jer svi SCD-i nisu ritmološke geneze te mogu biti posljedica reinfarkta ili rupture srca.

BIOMARKERI

Hagstrom i sur.[11] ispitivali su povezanost između koncentracije čimbenika rasta i faktora diferencijacije 15 (GDF-15) te učestalosti znatnih krvarenja i neželjenih kardiovaskularnih događaja u bolesnika s ACS-om randomiziranih u grupe liječenja tikagrelorom ili klopidogrelom u studiji PLATO (*PLATelet inhibition and patient Outcomes*). Primjenom statističkog modeliranja koje je bilo dodatno određeno za prilagodbu na temelju čimbenika kardiovaskularnog rizika i prognostičkih biomarkera (NT-proBNP, cistatin C, hsCRP, i hsTn), GDF-15 je bio povezan s povećanim rizikom od znatnih krvarenja i kombiniranih neželjenih događaja (kardiovaskularni mortalitet, spontani IM i moždani udar). Mehanizam za povezanost GDF-15 i rizik od krvarenja može biti povezan inhibitornim učincima aktivacije trombocita posredovane mehanizmom sličnim inhibiciji glikoproteinom IIb/IIIa, što može dovesti do niže sposobnosti stanica za trombogenezu. Navedeni podatci dalje podupiru primjenu tih biomarkera u ACS-u (**Slika 1**).

Liječenje

Mehanička reperfuzija infarktom pogođene arterije primjenom perkutane koronarne intervencije (PCI), uz pridruženu terapiju lijekovima koja uključuje antitrombotsku terapiju, ostaje temelj suvremenog liječenja ACS-a.

$P2Y_{12}$ INHIBITORI

Nedavno je prvi intravenski $P2Y_{12}$ inhibitor kangrelor registriran za upotrebu, proširujući spektar antitrombocitne terapije u

the Guidelines) database developed a multivariate hierarchical logistic regression model predicting in-hospital mortality. The population (243 440 patients from 655 hospitals) was divided into a 60% sample for model derivation, with the remaining 40% used for model validation. A simplified risk score was created to enable prospective risk stratification in clinical care. Age, heart rate, systolic blood pressure, presentation after cardiac arrest, presentation in cardiogenic shock, presentation in heart failure, presentation with ST-segment elevation MI, creatinine clearance, and Tn ratio were all independently associated with in-hospital mortality. Observed mortality rates varied substantially across risk groups, ranging from 0.4% in the lowest risk group (score <30) to 49.5% in the highest risk group (score >59). This work built upon and extended prior mortality risk models developed for patients with AMI. Although valuable for the selected populations at the time of their original development, changes in patient profiles and AMI management demand updating. The new risk score might serve this purpose.

In a pooled cohort analysis which merged individual data from 48 286 participants in 4 trials Hess *et al.*[10] found that sudden cardiac death (SCD) accounted for about one-third of CV deaths during 1-year follow-up and that reduced left ventricular ejection fraction, older age, diabetes mellitus, lower estimated glomerular filtration rate, higher heart rate, prior MI, peripheral artery disease, Asian race, male sex, and high Killip class were significantly associated with SCD. They also developed an integer-based score from this model, which yielded a calculated SCD probability ranging from 0.1 to 56.7%. This score might help in the identification of candidates for implantable cardioverter defibrillators above and beyond the mere assessment of ejection fraction although prospective assessment of device therapy is warranted because not all sudden death is arrhythmic and may in fact stem from other causes such as recurrent MI or cardiac rupture.

BIOMARKERS

Hagstrom *et al.*[11] assessed independent associations between growth differentiation factor-15 (GDF-15) levels and major bleeding and CV events in patients with ACS patients randomized to ticagrelor or clopidogrel in the PLATO (PLATelet inhibition and patient Outcomes) trial. In Cox proportional hazards models adjusting for established risk factors for CV disease and prognostic biomarkers (N-terminal pro B-type natriuretic peptide, cystatin C, high-sensitive C-reactive protein, and hsTn), GDF-15 was associated with increased risk of major bleeding and of the composite of CV death, spontaneous MI, and stroke. The mechanism for the association between GDF-15 and the risk of bleeding might be related to an inhibitory effect on platelet activation mediated via a mechanism similar to glycoprotein IIb/IIIa inhibition resulting in a lower ability of the cells to form a thrombus. These findings give further support to the utilization of this biomarker in the clinical setting of ACS (**Figure 1**).

Treatments

Mechanical reperfusion of the infarct-related artery by percutaneous coronary intervention (PCI) and adjunctive medical management including antithrombotic therapy remain the cornerstones of current ACS management.

$P2Y_{12}$ INHIBITORS

Recently the first intravenous $P2Y_{12}$ inhibitor, Cangrelor, was approved and broadened the armamentarium of antiplatelet

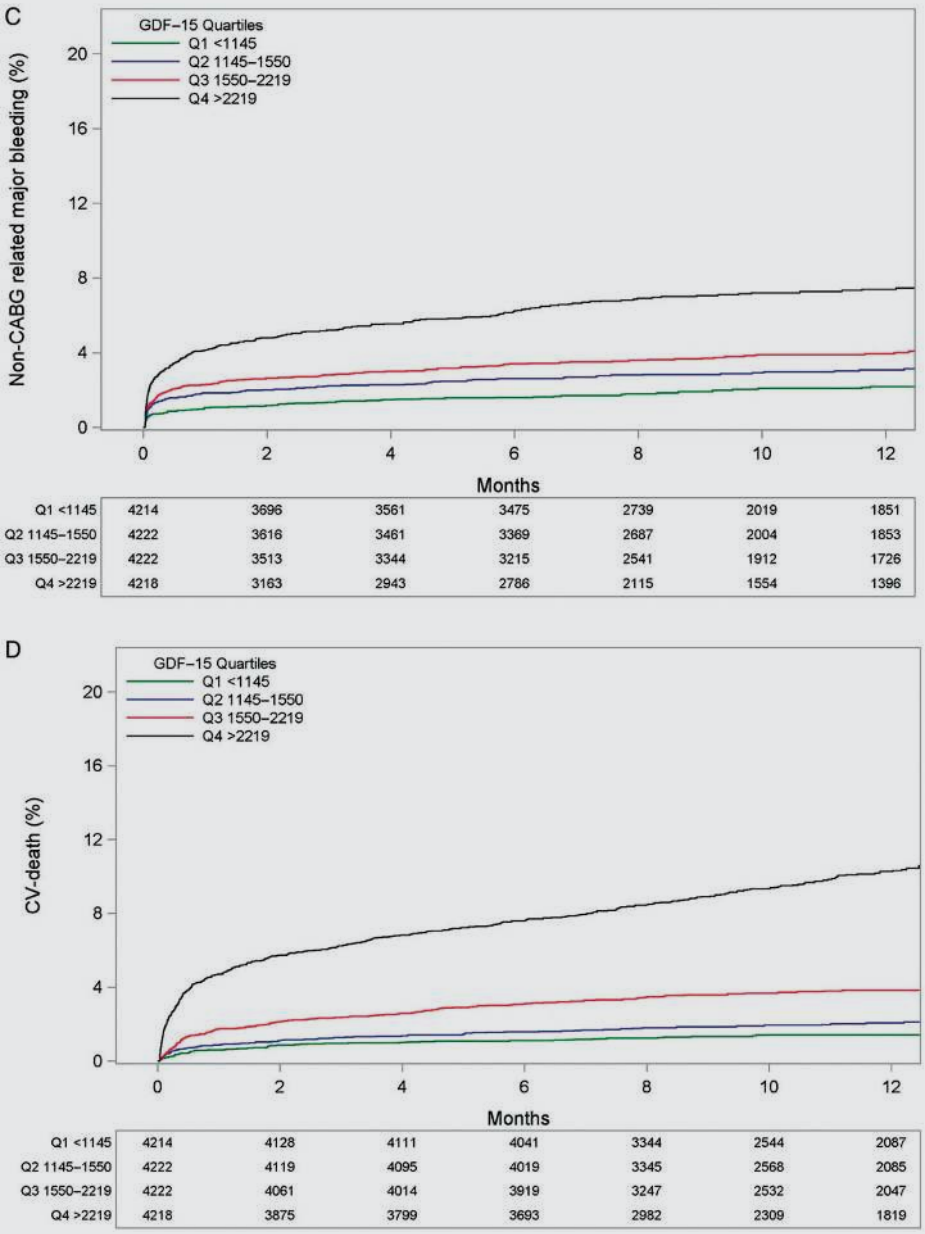

FIGURE 1. Kaplan–Meier estimated event rates of non-coronary artery bypass grafting-related major bleeding (top panel) and cardiovascular death (bottom panel) by quartiles of growth differentiation factor-15 (ng/L) assessed in 16 876 patients admitted with acute coronary syndrome.

CABG = coronary artery bypass grafting; CV = cardiovascular.

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bolesnika podvrgnutih PCI-ju. U studiji *CHAMPION PHOENIX*[12] *Gutierrez i sur.*[13] istraživali su utječe li radijalni ili femoralni pristup pri PCI-ju na efikasnost i sigurnost primjene kangrelora. Ukupno 11 415 bolesnika randomizirano je na primjenu kangrelora ili klopidogrela tijekom PCI-ja, a zajednički primarni ishod (smrtni ishod, infarkt miokarda, ishemijom vođena revaskularizacija ili tromboza stenta) (**Slika 2**) dogodila se u skupini s femoralnim pristupom u 4,8 % bolesnika uz terapiju kangrelorom nasuprot 6,0 % s klopidogrelom (*odds ratio*, OR [95% confidence interval, CI]: 0,79 [0,65 – 0,96]); u skupini s radijalnim pristupom primarni je ishod iznosio 4,4 % uz kangrelor nasuprot 5,7 % uz

agents in patients undergoing PCI. In the CHAMPION PHOENIX trial[12] Gutierrez *et al*.[13] analysed whether the femoral or radial approach for PCI interacted with the efficacy and safety of cangrelor. Among 11 145 patients randomly assigned to cangrelor or clopidogrel at the time of PCI the primary endpoint, a composite of death, MI, ischemia-driven revascularization, or stent thrombosis (**Figure 2**), occurred in the femoral cohort in 4.8% with cangrelor vs. 6.0% with clopidogrel (odds ratio, OR [95% confidence interval, CI]: 0.79 [0.65–0.96]); in the radial cohort, the primary endpoint was 4.4% with cangrelor vs. 5.7% with clopidogrel (OR [95% CI] 0.76 [0.54–1.06]). *P* for interaction

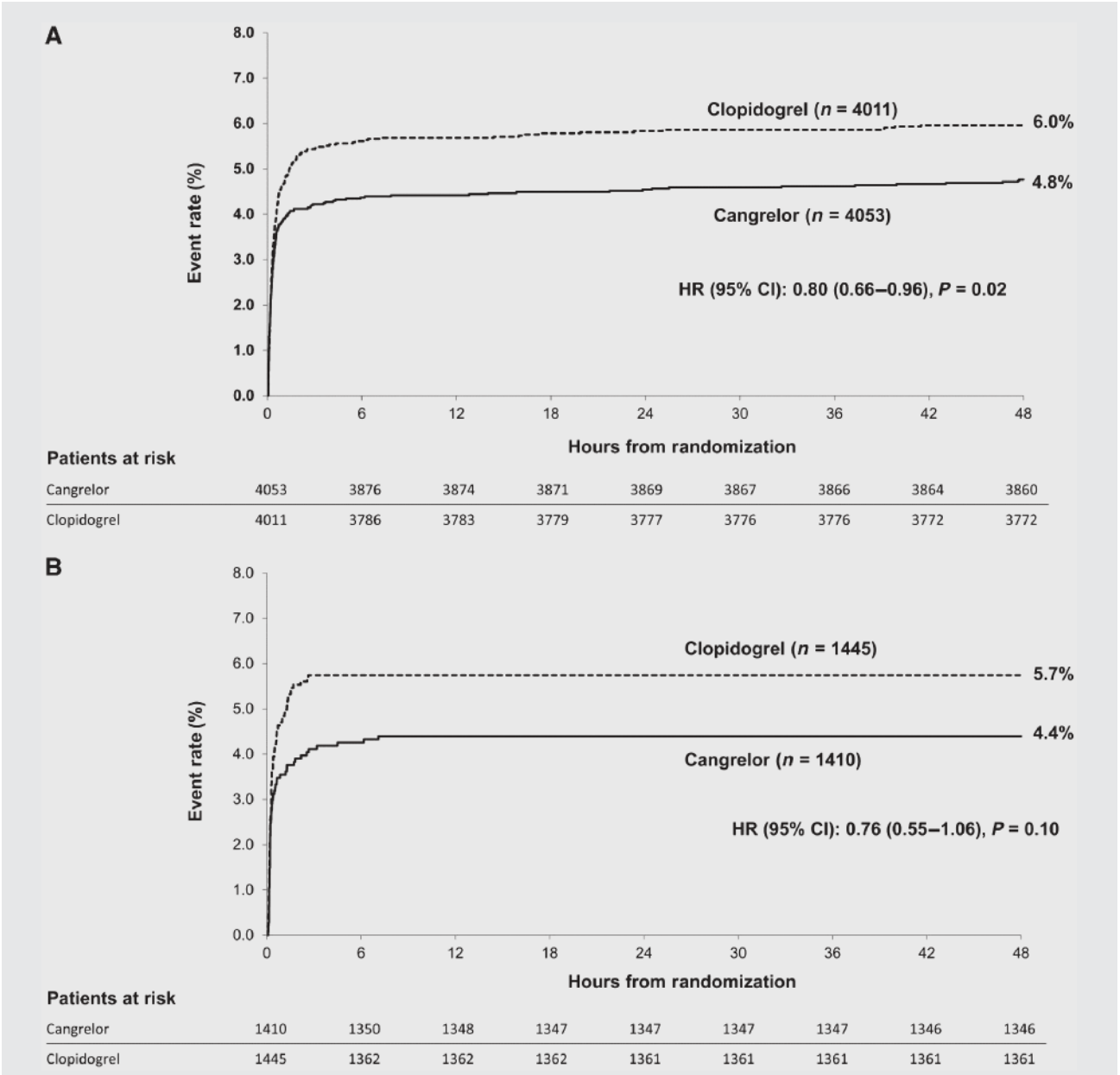

FIGURE 2. In the CHAMPION PHOENIX trial, Gutierrez *et al.*[13] analysed among 11 145 patients whether the femoral or radial approach for PCI interacted with the efficacy and safety of cangrelor. (*A*) Kaplan–Meier curves for the primary efficacy endpoint in the subgroup undergoing femoral access (cangrelor vs. clopidogrel). (*B*) Kaplan–Meier curves for the primary efficacy endpoint in the subgroup undergoing radial access (cangrelor vs. clopidogrel).

HR = hazard ratio; CI = confidence interval.

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klopidogrel (OR [95% CI] 0,76 [0,54 – 1.06]). P-vrijednost nije postigla značajnost. Apsolutna stopa učestalosti krvarenja bila je niža uz radijalni pristup.

Farmakokinetika i farmakodinamika peroralnih antitrombocitnih lijekova, pogotovo $P2Y_{12}$ inhibitora, može biti promjenjiva ovisno o apsorpciji lijeka i metabolizmu prvoga prolaska lijeka. Nadalje, interakcija između dvaju lijekova, između morfija i peroralnog inhibitora receptora $P2Y_{12}$ primijenjenih istodobno već je bila uočena.[14,15] U randomiziranoj dvostruko slijepoj

was not significant. The absolute rate of bleedings tended to be lower with radial access.

The pharmacodynamics and pharmacokinetics of oral antiplatelet drugs, particularly $P2Y_{12}$ inhibitors may be affected by absorption and first pass metabolism. Furthermore, a drug–drug interaction between morphine and oral $P2Y_{12}$ receptor inhibitors, when administered together, has been suggested.[14,15] In a randomized double-blind trial, Kubica *et al.*[16] investigated the pharmacokinetics and pharmacodynamics

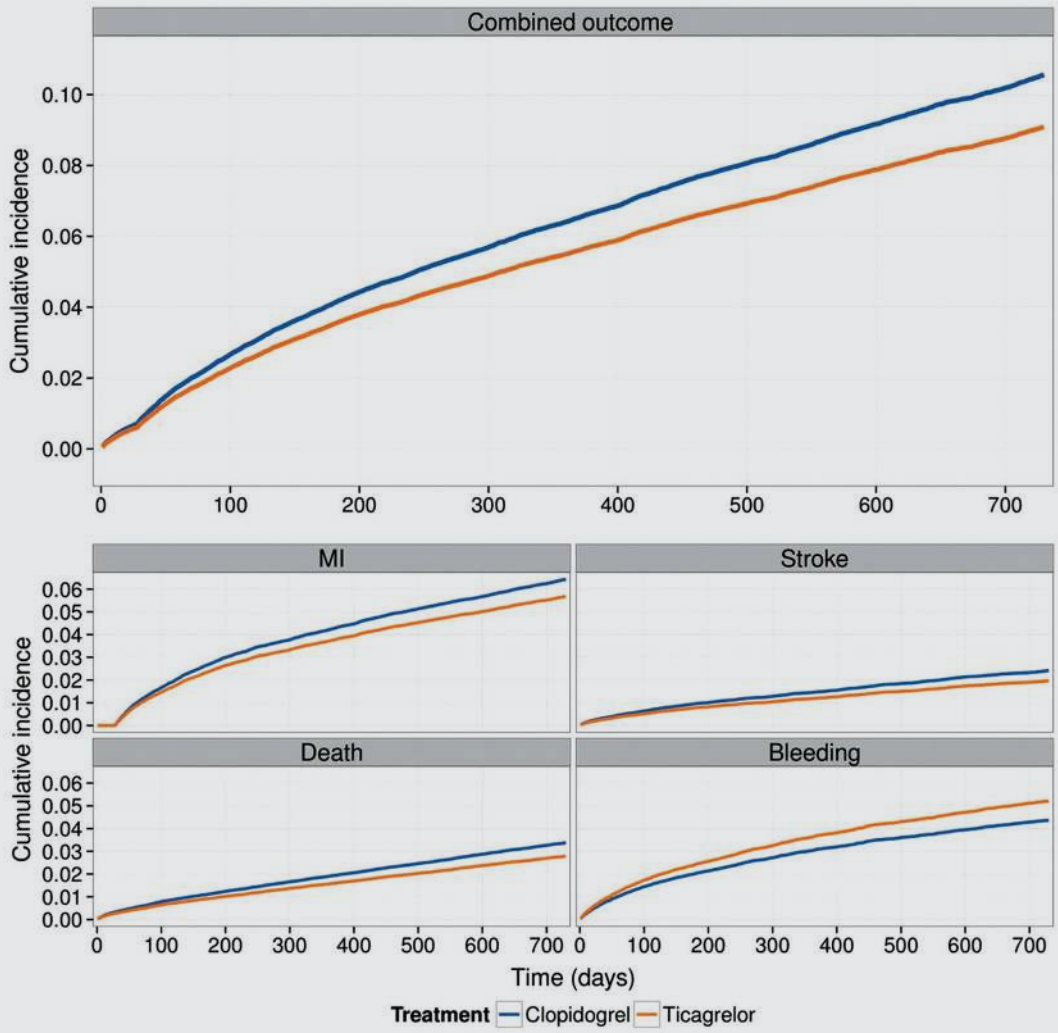

FIGURE 3. Incidence for the primary combined outcome of death, myocardial infarction, or stroke in 45 073 ACS patients from the SWEDEHEART registry. Bottom panels show the individual components of the primary outcome, as well as the primary bleeding outcome of hospitalization with bleeding (bottom right). Treatment with clopidogrel is shown in blue and ticagrelor in yellow.

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studiji, *Kubica i sur.*[16] istraživali su farmakokinetiku i farmakodinamiku tikagrelora kad je bio primijenjen s intravenskim morfijem ili bez njega u bolesnika s ACS-om. U 70 randomiziranih bolesnika morfij je snizio ukupno vrijeme izlaganja tikagreloru i aktivni metabolit za 36 % (AUC (0–12): 6307 prema 9791 ng h/mL; P = 0,003) i 37 %, odnosno (AUC(0–12): 1503 prema 2388 ng h/mL; P = 0,008). Usprkos ovoj znatnoj interakciji preostaje odrediti njezinu kliničku važnost.

Istodobno, analizom podataka iz registra SWEDEHEART[17] uspoređeni su ishodi bolesnika liječenih tikagrelorom u uspordbi s onima liječenima klopidogrelom. Nakon dvije godine liječenje tikagrelorom bilo je povezano s manjom učestalosti smrtnih ishoda (5,8 % prema 12,9 %, *adjusted hazard ratio* [HR] 0,83 [0,75 – 0,92]) i nižom stopom infarkta miokarda (6,1 % prema 10,8%, *adjusted* HR 0,89 [0,78 – 1,01]) u usporedbi s klopidogrelom (**Slika 3**). Ovi su podatci iz kliničke prakse konzistentni s rezultatima prethodno provedenih randomiziranih studija.[18]

of ticagrelor when administered with or without intravenous morphine in ACS patients. In 70 randomized patients, morphine lowered the total exposure to ticagrelor and its active metabolite by 36% (AUC (0–12): 6307 vs. 9791 ng h/mL; *P* = 0.003), and 37%, respectively (AUC(0–12): 1503 vs. 2388 ng h/mL; *P* = 0.008). Despite this impressive interaction, the clinical significance remains to be determined.

Concurrently, an analysis of 45 073 ACS patients from the SWEDEHEART registry[17] compared the outcomes of those treated with ticagrelor vs. those receiving clopidogrel. After 2 years, treatment with ticagrelor was associated with a lower rate of death (5.8% vs. 12.9%, adjusted hazard ratio [HR] 0.83 [0.75–0.92]) and a lower rate of MI (6.1 vs. 10.8%, adjusted HR 0.89 [0.78–1.01]) compared to clopidogrel (**Figure 3**). These real-world findings were consistent with previous randomized trial results.[18]

In STEMI patients undergoing primary PCI delayed antiplatelet effects of oral $P2Y_{12}$ inhibitors, including prasugrel,

U bolesnika sa STEMI-jem podvrgnutih intervenciji primarnim PCI-jem primijećen je odgođen antitrombocitni učinak peroralnih $P2Y_{12}$ inhibitora, uključujući prasugrel. *Rollini i sur.*[19] istraživali su bioraspoloživost usitnjene tablete prasugrela u usporedbi s cijelom tabletom. Studija je pokazala da, u usporedbi s cijelom tabletom, usitnjena tableta prasugrela smanjuje aktivnost $P2Y_{12}$ 30 minuta nakon uzimanja doze zasićenja, što perzistira i 1, 2, i 4 h nakon uzimanja lijeka. Stoga u bolesnika sa STEMI-jem podvrgnutih intervenciji PCI-jem usitnjena tableta prasugrela dovodi do brže apsorpcije lijeka i. posljedično. bržeg i potentnijeg antitrombocitnog učinka u usporedbi s ingestijom cijele tablete. Koliko bi ova zapažanja mogla biti povezana s kliničkim ishodima (npr. akutnom trombozom stenta) trebalo bi potvrditi većim skupinama ispitanika.

OPTIMALNO TRAJANJE DVOJNE ANTITROMBOCITNE TERAPIJE

Optimalno trajanje dvojne antitrombocitne terapije (DAPT) nakon PCI-ja kod ACS-a neprekidno je predmet debate jer bi bolesnici procijenjeni na one s visokim rizikom od krvarenja mogli imati koristi od skraćenja trajanja DAPT. Suprotno tomu, ponavljani ishemijski događaji kod stabilnih bolesnika nakon ACS-a mogli bi biti reducirani produženjem trajanja DAPT dulje od godine dana, što su sugerirale metaanalize.[20] No, velika krvarenja događaju se mnogo češće ako je DAPT prolongirana.

U randomiziranoj studiji stent obložen lijekom biolimus-A (DCS) pokazao je bolje ishode s DAPT-om trajanja samo mjesec dana u usporedbi s običnim (BMS) stentom u bolesnika s visokim rizikom od krvarenja.[21] Podanaliza usmjerna na bolesnike s ACS-om[22] bila je u skladu s ukupnim rezultatima. U 12-mjesečnom praćenju, liječenje DCS stentom u ACS-u bilo je efikasnije (kliničkom slikom vođena revaskularizacija ciljne lezije 3,9 % prema 9,0 %; P = 0,009) i sigurnije (zajednička incidencija srčane smrti, infarkta miokarda, potvrđene ili vjerojatne tromboze stenta 9,3 % prema 18,5 %, P = 0,001) nego liječenje s BMS stentom usprkos jednomjesečnoj DAPT u objema grupama (**Slika 4**). Kako je DCS pokazao bolju učinkovitost i bolji sigurnosni profil, uporaba BMS stenta u liječenju stenoze koronarnih arterija trebala bi biti upitna. Međutim, niža cijena BMS stenta poticajan je argument u područjima s ograničenim novčanim sredstvima.

BIVALURIDIN

U primarnoj PCI intervenciji za akutne infarkte miokarda sa ST elevacijom, studija HORIZONS[23] prije je pokazala smanjenu smrtnost uz bivaluridin u usporedbi s heparinom uz inhibitore glikoproteinskih receptora (GPI). Studije koje su slijedile[24-27], uspoređujući bivaluridin s drugim antitrombotskim strategijama, pokazale su različite rezultate. Nova analiza podataka 61 136 bolesnika iz kliničke prakse iz nacionalnog registra UK PCI[28] od 2008. do 2012. godine nije pokazala znatnu razliku u kratkoročnom i srednjoročnom praćenju smrtnosti između bolesnika sa STEMI-jem koji su bili liječeni bivaluridinom u usporedbi s onima liječenima heparinom uz GPI inhibitore tijekom primarnog PCI-ja. Potrebne su veće randomizirane studije za pozicioniranje uloge bivaluridina u odnosu na uporabu heparina tijekom primarne PCI intervencije.

BETA-BLOKATORI

Utjecaj intravenske primjene beta-blokatora prije primarnog PCI-ja na kliničke ishode i veličinu infarkta miokarda nije dobro potvrđena. U *post hoc* analizi studije METOCARD-CNIC[29] pretpo-

have been observed. Rollini *et al.*[19] investigated the bioavailablity of crushed prasugrel tablets vs. whole prasugrel tablets. The study showed that compared with whole tablets, crushed prasugrel led to reduced $P2Y_{12}$ reaction units by 30 min post-loading dose, which persisted at 1, 2, and 4 h post-loading dose. Thus, in STEMI patients undergoing primary PCI, crushed prasugrel leads to faster drug absorption, and consequently, more prompt and potent antiplatelet effects compared with whole tablet ingestion. Whether this observation may be associated with clinical endpoints (e.g. acute stent thrombosis) needs to be determined in larger cohorts.

OPTIMAL DUAL ANTIPLATELET TREATMENT DURATION

The optimal duration of DAPT after PCI in the setting of ACS is continuously debated as patients considered at high risk of bleeding may benefit from a shortened DAPT duration. In contrast, subsequent ischemic events in stable post ACS patients may be reduced by prolonged DAPT beyond 1 year, as was suggested in a meta-analysis.[20] However, major bleeding occurs significantly more often under prolonged DAPT.

In a randomized trial, a Biolimus-A9 drug coated stent (DCS) has shown better outcomes with only one month DAPT compared to a bare metal stent (BMS) in patients at high-bleeding risk.[21] A sub-study focusing on patients with ACS[22] was consistent with the overall findings. At 12-month follow-up, treatment with the DCS in ACS patients was more effective (clinically driven target-lesion revascularization 3.9% vs. 9.0%, P = 0.009) and safer (cumulative incidence of cardiac death, MI, or definite or probable stent thrombosis 9.3% vs. 18.5%, P = 0.001), than the BMS despite one month DAPT in both groups (**Figure 4**). As the DCS exhibited a better safety and efficacy profile than BMS, the use of BMS has to be questioned for the treatment of coronary artery stenosis. However, the lower cost of the BMS is a favourable argument in an environment with limited resources.

BIVALIRUDIN

In primary PCI for ST-segment elevation MI (STEMI), the HORIZONS trial[23] had previously shown a mortality benefit for bivalirudin over heparin with glycoprotein inhibitors (GPI). Subsequent trials[24–27] comparing bivalirudin with other antithrombotic strategies rendered divergent results. Now a real-world analysis of 61 136 patients from the UK national PCI registry[28] from 2008 to 2012 showed no significant difference in short- or medium-term mortality between STEMI patients treated with bivalirudin vs. heparin and GPI at primary PCI. Larger randomized trials will be needed to settle the role of bivalirudin vs. heparin in primary PCI.

BETA-BLOCKADE

The impact of intravenous beta-blockers before primary PCI on clinical outcomes and infarct size is not well established. A post hoc analysis from the METOCARD-CNIC trial[29] suggested that the sooner metoprolol is administered in the course of an STEMI, the smaller the infarct size. However, the Early-BAMI trial[30] did not show any difference between STEMI patients randomized to early intravenous metoprolol or placebo. In this study, metoprolol reduced the incidence of malignant arrhythmias in the acute phase but was not associated with a reduction in the infarct size (peak and area under the creatine kinase curve).

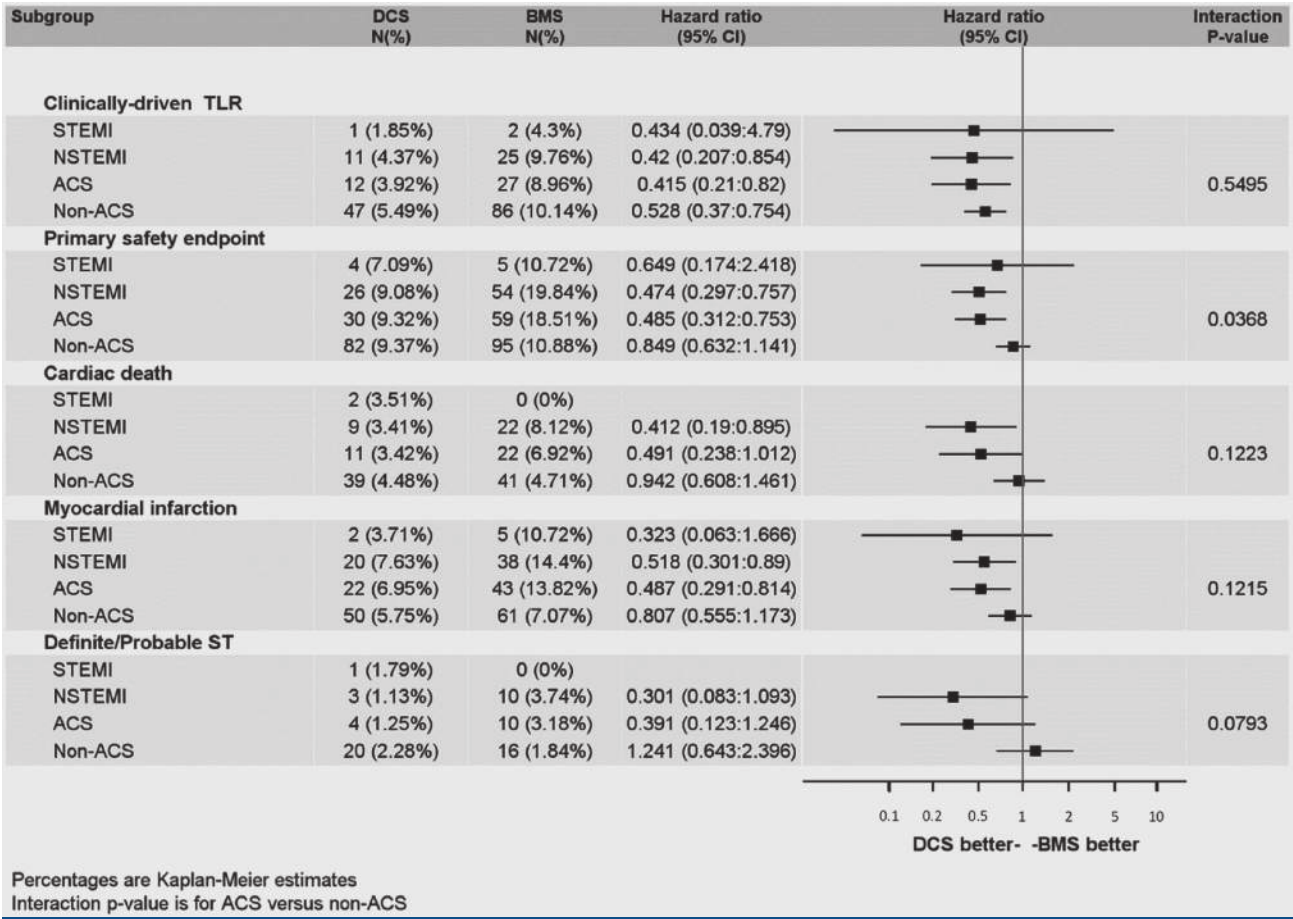

FIGURE 4. In a randomized trial a Biolimus-A9 drug coated stent showed better outcomes with only 1-month dual antiplatelet therapy compared to a bare metal stent, in patients at high-bleeding risk. This sub-study focusing on patients with ACS was consistent with the overall findings. The benefit of the drug coated stent over the bare metal stent was consistent across various sub-groups.

ACS = acute coronary syndrome; BMS = bare metal stent; DCS = drug coated stent; NSTEMI = non-ST-elevation myocardial infarction; ST = stent thrombosis; STEMI = ST-elevation myocardial infarction; TLR = target lesion revascularization.

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stavlja se da ranija primjena metoprolola tijekom STEMI-ija dovodi do manje veličine infarciranog miokarda. Međutim, studija *Early-BAMI*[30] nije pokazala nikakvu razliku između bolesnika sa STEMI-jem randomiziranih na ranu intravensku primjenu metoprolola ili placeba. U ovoj je studiji metoprolol smanjio incidenciju malignih aritmija u akutnoj fazi, ali se nije dokazala povezanost sa smanjenjem veličine infarcirane zone (vršak vrijednosti i površina pod krivuljom kreatinin-kinaze).

LIJEKOVI KOJI SNIZUJU VRIJEDNOSTI LIPIDA

Farmakoterapija kojom se smanjuju vrijednosti lipoproteina male gustoće (LDL) u krvi je pokazala postojanu dobrobit za kardiovaskularne ishode u bolesnika s koronarnom bolesti srca. Analizom studije IMPROVE-IT dodatak ezetimiba simavastatinu nije samo smanjio učestalost prvih primarnih ishoda nego je smanjio i učestalost ponovljenih nepovoljnih kardiovaskularnih ishoda u bolesnika s ACS-om.[31] U međuvremenu nova klasa lijekova – inhibitora proproteina konvertaze subtilisin/kexin tip 9, koja je odobrena za liječenje bolesnika s obiteljskom hiperkolesterolemijom, u fazi je ispitivanja u bolesnika s ACS-om (*ClinicalTrials.gov* Identifier: NCT01663402).

LIPID LOWERING AGENTS

Pharmacotherapy that reduces low-density lipoprotein cholesterol has consistently shown benefit for CV endpoints in patients with coronary artery disease. In an analysis of the IMPROVE-IT trial, the addition of ezetimibe to simvastatin not only reduced the rate of first primary endpoint but also reduced the rate of subsequent adverse CV endpoints in ACS patients.[31] Meanwhile a new class of agents—proprotein convertase subtilisin/kexin type 9 inhibitors, which are approved for the treatment of familiar hypercholesterolemia, are under investigation in ACS patients (ClinicalTrials.gov Identifier: NCT01663402).

FIBRINOLYSIS IN NON-PCI CAPABLE HOSPITALS

The preferred reperfusion strategy for ACS patients presenting with STEMI is primary PCI. However, systemic fibrinolysis is still applied in STEMI patients in non-PCI capable hospitals if transfer for primary PCI would lead to unacceptable reperfusion delays. In a prospective multicentre STEMI registry, Carrillo *et al.*[32] compared the effect of in situ fibrinolysis vs. PCI transfer on 30-day mortality in a real-life consecutive cohort of 2470

FIBRINOLIZA U BOLNICAMA BEZ MOGUĆNOSTI PERKUTANE KORONARNE INTERVENCIJE

Primarni PCI terapija je izbora u ACS bolesnika sa STEMI-jem. Međutim, sistemna fibrinoliza još se uvijek primjenjuje u bolesnika sa STEMI-jem u bolnicama bez mogućnosti intervencije primjenom PCI-ja u slučajevima kad bi transport do centra u kojemu postoji mogućnost PCI-ja uzrokovao neprihvatljivo kašnjenje u reperfuzijskom liječenju. U prospektivnom multicentričnom registru *Carrillo i sur.*[32] uspoređivali su učinak liječenja fibrinolizom nasuprot transferu do PCI centra na 30-dnevni mortalitet u skupini od 2470 bolesnika sa STEMI-jem. Studija je pokazala je u bolesnika koji su transportirani, a čije je vrijeme od prvoga medicinskog kontakta (FMC) do intervencije (PCI) postignuto unutar 140 minuta, dokazana povezanost sa znatno nižom smrtnosti (2,0 % u vrijeme prvog kontakta do intervencije < 99 min i 4,6 % u vrijeme prvog kontakta do intervencije 99 – 140 min; P = 0,01 i P = 0,03, u usporedbi s fibrinolizom). U analizi logističkom regresijom, reperfuzija fibrinolizom bila je neovisni prediktivni čimbenik smrtnosti nakon 30 dana (OR: 1,91, 95 % CI: 1,01–3,50; P = 0,04). Ovi rezultati upućuju na to da se preporučuje transfer do PCI centra ako je vrijeme od FNC-a do PCI-ja kraće od 140 min.

STRATEGIJE REVASKULARIZACIJE U AKUTNOME KORONARNOM SINDROMU

Trećina do polovice bolesnika s ACS-om ima višežilnu koronarnom bolest srca. Najbolja strategija liječenja i optimalno vrijeme za PCI ostalih značajnih lezija i dalje su predmet rasprave. U studiji SMILE[33] 584 bolesnika s NSTEMI-jem s višežilnom koronarnom bolesti bili su randomizirani na kompletnu revaskularizaciju tijekom jedne intervencije ili na kompletnu revaskularizaciju u više faza tijekom iste hospitalizacije. Nisu registrirane znatne razlike u incidenciji jednogodišnje srčane smrti (3,41 % prema 5,32 %, odnosno P = 0,27) ni infarkta miokarda (2,65 % prema 3,8 %, odnosno P = 0,46) između tih dviju grupa, iako je ponovna revaskularizacija ciljne lezije bila veća u grupi revaskulariziranoj u više faza (8,33 % prema 15,2 %, P = 0,01). Međutim, nije se dokazalo ukupno bolje preživljenje u usporedbi kompletne revaskularizacije u jednoj ili višefaznoj intervenciji.

Ako se ciljna lezija za ACS nalazi u nezaštićenom deblu lijeve koronarne arterije, optimalna je revaskularizacija predmet rasprava. U multinacionalnom registru DELTA[34] , koji je pratio sve liječene bolesnike, istraživani su dugoročni ishodi bolesnika s ACS-om s nezaštićenim deblom liječenih aortokoronarnim premosnicama (CABG) i onih liječenih PCI intervencijom. U 379 bolesnika nisu nađene znatne razlike u skupnim ishodima ukupne smrtnosti, akutnom infarktu miokarda i cerebrovaskularnim incidentima. Kako su bolesnici u ovoj studiji dobivali stentove iz prve generacije DES, mogla bi se očekivati i niža stopa ponovljene revaskularizacije ciljne lezije primjenom stentova novije generacije.

LIJEČENJE STARIJIH OSOBA

Schoenenberger i sur.[35] analizirali su primjenu terapije preporučene u smjernicama i unutarbolničke ishode 13 662 bolesnika s ACS-om i dobi ≥70 godina uključenih u prospektivne kohorte iz studije AMIS (*Acute Myocardial Infarction in Switzerland*) tijekom četverogodišnjih razdoblja (2001. – 2004., 2005. – 2008., i 2009. – 2012.). Između prvog i zadnjeg četverogodišnjeg razdoblja povećala se primjena PCI-ja i lijekova preporučenih prema smjernicama. Istodobno, unutarbolnička smrtnost ukupne populacije smanjila se s 11,6 % u prvom na 10,0 % u posljednjemu četverogodišnjem razdoblju i broj unutarbolničkih velikih

STEMI patients. The study showed that patients in the transfer group whose from first medical contact (FMC) to device (PCI) time was achieved within 140 min were associated with significantly lower mortality (2.0% for FMC-device < 99 min, and 4.6% for FMC-device 99–140 min; *P* = 0.01 and *P* = 0.03, respectively vs. fibrinolysis). In multivariable logistic regression analysis, reperfusion with fibrinolysis was an independent 30-day mortality predictive factor (OR: 1.91, 95% CI: 1.01–3.50; *P* = 0.04). These results suggest, that transfer to a PCI-capable hospital should be recommended, if FMC-device delay is less than 140 min.

REVASCULARIZATION STRATEGIES IN ACS

A third to half of ACS patients present with multi-vessel disease. The best treatment strategy and the optimal timing for non-culprit lesion PCI in ACS is a matter of debate. In the SMILE trial,[33] 584 patients with non ST elevation MI with multi-vessel disease were randomized to single-stage complete revascularisation vs. multi-stage complete revascularization during the same hospitalization. No significant difference in the one-year incidence of cardiac death (3.41% vs. 5.32% respectively, *P* = 0.27) and MI (2.65% vs. 3.8% respectively, *P* = 0.46) was found between groups, although target vessel revascularisation was higher in the multi-stage group (8.33% vs. 15.2%, *P* = 0.01). However, there was no overall survival benefit of single- vs. multi-staged complete revascularisation.

If the culprit lesion of an ACS is located in an unprotected left main coronary artery (ULMCA), the optimal revascularization strategy is a matter of debate. In the DELTA all-comer, multinational registry[34] the long-term outcomes of ACS patients with ULMCA treated with coronary artery bypass grafting (CABG) or PCI was investigated. In 379 ACS patients, no significant differences emerged for the composite endpoint of all-cause death, AMI, and cerebrovascular accident. As patients in this study received first-generation drug eluting stents a lower rate of target vessel revascularisation may be expected with newer-generation stents.

TREATMENT OF THE ELDERLY

Schoenenberger *et al.*[35] analysed the use of guideline-recommended therapies and in-hospital outcomes of 13 662 ACS patients ≥70 years enrolled in the prospective Acute Myocardial Infarction in Switzerland (AMIS) cohort according to 4-year periods (2001–2004, 2005–2008, and 2009–2012). Between first and last 4-year period, PCI use increased as well as use of guideline recommended drugs. At the same time, in-hospital mortality of the overall population decreased from 11.6% in the first to 10.0% in the last 4-year period, and in-hospital major adverse cardiac and cerebrovascular events from 14.4 to 11.3%. This study indicates that increasing use of guideline-recommended therapies is appropriate in the elderly. It remains to establish whether this notion is also valid for octogenarians.

One aspect in the very elderly population was investigated by Tegn *et al.*[36] They studied whether patients aged 80 years or older presenting with an ACS without ST-segment elevation would benefit from an early invasive strategy compared to an initially conservative management. During a median follow-up of 1.53 years, the primary outcome, a composite of MI, need for urgent revascularization, stroke, and death, occurred in 93 (40.6%) of 229 patients assigned to the invasive group and 140 (61.4%) of 228 patients assigned to the conservative group (HR 0.53 [95% CI 0.41–0.69], *P* = 0.0001). The two strategies did

nepovoljnih srčanih i cerebrovaskularnih događaja smanjio se s 14,4 na 11,3 %. Ova sudija pokazuje da je sve veća primjena liječenja prema smjernicama prikladna za starije osobe. Preostaje utvrditi vrijedi li ova spoznaja i za osobe starije od 80 godina.

Jedan od aspekata liječenja kod vrlo stare populacije istraživali su *Tegn i sur.*[36] Oni su pratili bi li bolesnici stariji od 80 godina koji su se prezentirali kao ACS bez elevacije ST segmenta imali dobrobit od rane invazivne strategije liječenja u usporedbi s inicijalnom konzervativnom strategijom liječenja. Tijekom medijana praćenja od 1,53 godine primarni ishodi (zbroj infarkta miokarda, potrebe za žurnom revaskularizacijom, moždanih udara i smrtnih ishoda) dogodili su se u 93 (40,6 %) od 229 bolesnika iz invazivne grupe i u 140 (61,4 %) od 228 bolesnika iz konzervativno liječene grupe (HR 0,53 [95 % CI 0,41 – 0,69], P = 0,0001). Dva se načina liječenja nisu razlikovala što se tiče komplikacija vezanih za krvarenje. U zaključku, u skladu sa smjernicama ESC-a,[37] invazivna strategija liječenja u bolesnika starijih od 80 godina ili starijih, koji boluju od NSTEMI-ja, bila je superiornija u usporedbi s konzervativnom strategijom liječenja.

MEHANIČKA CRPKA ZA POTPORU LIJEVE KLIJETKE

Bolesnicima s akutnim zatajivanjem srca ili kardiogenim šokom refraktornim na reperfuziju i medikamentno liječenje mogla bi zatrebati i mehanička cirkulatorna potpora. U registru INTERMASC bolesnici s ugrađenom trajnom mehaničkom crpkom (VAD) tijekom ACS-a uspoređeni su s bolesnicima, koji imaju VAD zbog indikacije koja nije AKS.[38] U jednoj neusklađenoj analizi skupina bolesnika s ACS-om imala je u ranoj fazi veći rizik (HR: 1,24; P = 0,04), ali smanjen rizik od smrti u kasnoj fazi (HR: 0,57; P = 0,04) od grupe bez AKS-a. Usprkos tomu što su bolesnici bili teže bolesni prije implantacije VAD-a, bolesnici s ACS-om imali su slične ishode kao i oni bez AKS-a. Stoga je implantacija VAD uređaja vrijedna strategija liječenja u ACS bolesnika s kardiogenim šokom ili zatajivanjem srca refraktornim na medikamentno liječenje.

Ishodi liječenja u specifičnim grupama bolesnika

ŽENE

Zanimljivo znanstveno priopćenje Američkoga kardiološkog društva o ACS-u u žena[39] saželo je glavne razlike između muškaraca i žena u ovom kliničkom scenariju. Posebice je naglašeno da, neovisno o dobi, unutar godine dana od prvog infarkta miokarda umire više žena nego muškaraca; unutar pet godina od prvog infarkta miokarda umire više žena nego muškaraca, imaju češće zatajivanje srca ili dožive moždani udar, a veći mortalitet u žena u usporedbi s muškarcima dijelom je objašnjen različitim čimbenicima rizika, kliničkom slikom i liječenjem. Zapravo je prevalencija šećerne bolesti, zatajivanja srca, arterijske hipertenzije, depresije i bubrežne disfunkcije veća u žena nego u muškaraca. Uspoređujući ih s muškarcima, žene se češće prezentiraju NSTEMI-jem i neopstruktivnom koronarnom bolesti. U žena se češće vide neuobičajeni patofiziološki mehanizmi ACS-a kao što su spontana disekcija ili spazam koronarne arterije.

PUŠAČI

Symons i sur.[40] pratili su učinak pušenja u 471 bolesnika sa STEMI-jem oslikavanjem magnetnom rezonancijom srca. Pušenje je bilo povezano s intramiokardijalnom hemoragijom (IMH) od početka, čak i nakon korekcije učinaka ostalih čimbenika povezanih s ishemijsko-reperfuzijskom ozljedom. Neočekivano not differ in terms of bleeding complications. In conclusion, in line with the ESC Guidelines,[37] an invasive strategy in patients aged 80 years or older presenting with non-ST segment elevation MI was superior to a conservative strategy.

LEFT VENTRICULAR ASSIST DEVICE

Patients who present with acute heart failure or cardiogenic shock refractory to reperfusion and medication may require mechanical circulatory support. In the INTERMACS registry patients who received a durable ventricular assist device (VAD) in the setting of an ACS were compared to those who received a VAD for non-ACS indications.[38] In an unadjusted analysis the ACS group had higher early phase hazard (HR: 1.24; *P* = 0.04) but reduced late-phase hazard of death (HR: 0.57; *P* = 0.04) than the non-ACS group. Despite being more critically ill before VAD implantation, ACS patients had similar outcomes compared to non-ACS patients. Therefore, VAD implantation is a valuable strategy in ACS patients with cardiogenic shock or heart failure refractory to medical therapy.

Outcomes in specific patient populations

WOMEN

An interesting scientific statement from the American Heart Association on ACS in women[39] summarizes the main differences between men and women in this setting. In particular, it is highlighted that regardless of age, within a year of a first AMI, more women than men die; within 5 years of a first AMI, more women than men die, have heart failure, or suffer from a stroke, although the higher mortality for women compared with men is explained partially by differences in risk factors, clinical presentation, and treatment. Indeed, the prevalence of diabetes mellitus, heart failure, hypertension, depression, and renal dysfunction is higher in women compared with men. Compared with men, women more commonly present with NSTEMI and non-obstructive coronary artery disease. Women are also more likely to have unusual pathophysiological mechanisms of ACS such as spontaneous coronary artery dissection or coronary artery spasm.

SMOKERS

Symons *et al.*[40] assessed the effect of smoking in 471 STEMI patients by cardiac magnetic resonance. Smoking was associated with intramyocardial haemorrhage (IMH) at baseline even after correction for other factors associated with ischemia-reperfusion injury. Unexpectedly, smoking was an independent protective predictor against adverse left ventricular remodelling consistent with the 'smoker's paradox', although the presence of IMH at baseline abolished this paradoxical, beneficial effects of smoking. It remains to establish what mediates these intriguing protective effects of smoking in STEMI in order to identify new therapeutic targets.

RHEUMATOID ARTHRITIS

Despite a wealth of studies describing an increased incidence of ACS in rheumatoid arthritis (RA), considerably less is known about the clinical characteristics and their association with short-term outcome of such ACS. Mantel *et al.*[41] compared the clinical presentation of incident ACS in a cohort of 1135 subjects with prevalent RA and in a cohort of 3184 matched general population comparators. RA subjects more

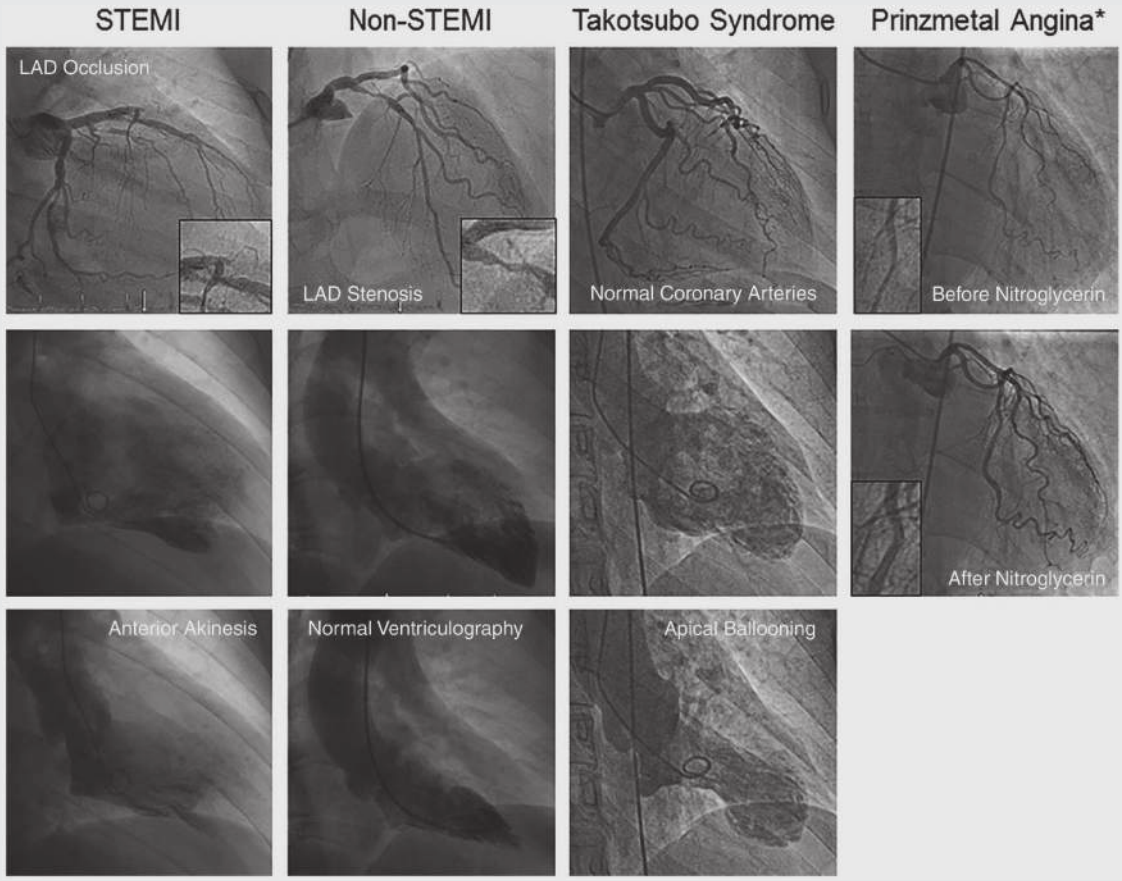

FIGURE 5. Typical angiographic presentation of ST-segment elevation myocardial infarction (STEMI), non-STEMI, Takotsubo syndrome, and Prinzmetal angina.

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no, pušenje je bilo neovisni zaštitni faktor nepovoljnog remodeliranja lijeve klijetke sukladno „pušačkom paradoksu", iako je prisutnost inicijalno prisutnih IMH-a poništila ovaj povoljni paradoksalni učinak pušenja. Preostaje utvrditi što pridonosi ovom intrigirajućem protektivnom učinku pušenja u bolesnika sa STEMI-jem radi pronalaženja novih terapijskih ciljeva.

REUMATOIDNI ARTRITIS

Usprkos doprinosu studija koje su opisale povećanu incidenciju ACS-a u bolesnika s reumatoidnim artritisom (RA), mnogo su manje poznata klinička obilježja i njihova povezanost s kratkoročnim ishodima u ACS-u. *Mantel i sur.*[41] uspoređivali su kliničku sliku ACS-a u kohorti od 1135 bolesnika s poznatim RA i kohorte od 3184 usporedivih bolesnika iz opće populacije. Bolesnici s RA češće su se prezentirali iznenadnom smrću, STEMI-jem, višim vrijednostima hsTn i većom učestalošću unutarbolničkih komplikacija u usporedbi s onima iz opće populacije.

VAZOSPASTIČNA ANGINA

Ahn i sur.[42] uspoređivali su ishode 188 bolesnika s vazospastičnom anginom i spriječenom iznenadnom srčanom smrću i 1844 bolesnika s vazospastičnom anginom bez doživljene spriječene iznenadne srčane smrti, uključenih iz 13 centara u Južnoj Koreji. Prva je skupina imala mnogo već rizik od druge skupine. Prediktori iznenadne srčane smrti uključivali su dob,

frequently presented with SCD, STEMI, had higher levels of hsTn and higher frequencies of in-hospital complications compared with the general population comparators. Furthermore, the short-term mortality was higher among RA-associated ACS. The higher risk of RA-associated ACS is consistent with the important role of inflammation in the pathogenesis of ACS and should stimulate further research for the identification of personalized forms of treatment.

VASOSPASTIC ANGINA

Ahn *et al.*[42] compared the outcomes of 188 patients with vasospastic angina and aborted SCD and 1 844 patients with vasospastic angina without aborted SCD enrolled from 13 heart centres in South Korea. The former had a much higher risk of death than the latter. Predictors of SCD included age, hyperlipidaemia, family history of SCD, multi-vessel spasm, and left anterior descending artery spasm. It remains to establish which mechanisms make the myocardium more susceptible to malignant arrhythmias in these patients.

TAKOTSUBO SYNDROME

Finally, an emerging notion is that ACS are not only caused by epicardial anatomic or functional alterations but also by coronary microvascular dysfunction (**Figure 5**). This seems to be the case, in particular for takotsubo cardiomyopathy

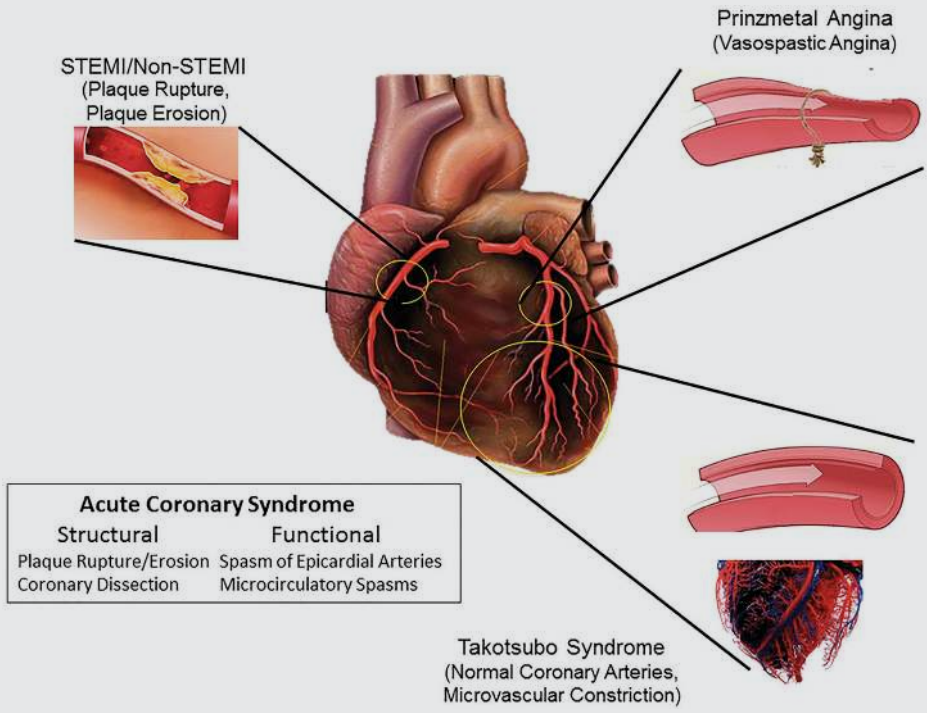

FIGURE 6. Macrovascular and microvascular ischemia in patients with ST-segment elevation myocardial infarction (STEMI), non-STEMI, Takotsubo syndrome and Prinzmetal angina, respectively.

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hiperlipidemiju, obiteljsku anamnezu iznenadne srčane smrti, spazam više krvnih žila i spazam lijeve prednje silazne arterije. Preostaje utvrditi koji mehanizam čini miokard podložnijim pojavi malignih aritmija u ovakvih bolesnika.

TAKO-TSUBO SINDROM

U konačnici, novija je spoznaja da akutni koronarni sindrom nije uzrokovan samo promjenama u anatomiji i funkciji epikardijalnih krvnih žila već i disfunkcijom koronarne mikrovaskulature (**Slika 5**). To je, čini se, posebice slučaj za Tako-tsubo kardiomiopatiju (TTC)[43] (**Slika 6**). U tom pogledu, jedna je studija pokazala da TTC može biti potaknuta ne samo negativnim već i pozitivnim životnim događajima.[44] Dok su karakteristike bolesnika, ali isto tako kratkoročni i dugoročni ishodi, bili slični između dviju grupa, TTC srednjeg dijela klijetke bila je učestalija kod „sretnih srca" u odnosu prema onima „tužnih srca". Vjerojatno je da usprkos razlici u vrsti događaja, sretni i tužni događaji dijele sličan zajednički krajnji emocionalni put koji u konačnici može uzrokovati TTC.

Perspektive

Veliki je napredak postignut u razumijevanju ACS-a. Posebice noviji podatci upućuju na to da bi bazofili i eozinofili mogli imati ulogu u patogenezi ACS-a upozoravajući na nove potencijalne ciljeve liječenja. Daljnji su napori također potrebni u ranoj dijagnostici ACS-a, kada ostane nedefiniran usprkos optimalnoj uporabi Tn u procjeni. Dokaz da GDF-15 ima prediktivnu vrijednost za ishemijski rizik, ali i rizik od krvarenja vrlo je zanimljiv, iako njegova uloga u svakodnevnoj praksi tek treba biti potvr-

(TTC)[43] (**Figure 6**). To this regards, one study illustrated that TTC can be triggered by not only negative but also positive life events.[44] While patient characteristics and also short- and long-term outcomes were similar between groups, the mid-ventricular TTC type was more prevalent among the 'happy hearts' than among the 'broken hearts'. Presumably, despite their distinct nature, happy and sad life events may share similar final common emotional pathways, which can ultimately trigger TTC.

Perspectives

Major progress has been made in the understanding of ACS. In particular, novel data indicate that both basophils and eosinophils may play a pathogenetic role in ACS suggesting new potential therapeutic targets. Further efforts are also needed in the early diagnosis of ACS when it remains undetermined after optimal Tn assessment. The demonstration that GDF-15 predicts both ischemic and bleeding risk is exciting although its role in daily practice remains to be established. With regards to antithrombotic treatment, it remains challenging to tailor DAPT duration according to individual risk. Finally, the worse outcome of patients with RA as compared to those without RA indicates that the former need more aggressive forms of treatment to be defined in future studies.

CONFLICT OF INTEREST: F. Crea has received speaker fees from Astra Zeneca and Servier. R.K. Binder has received speakers fees from Astra-Zeneca, is consultant for Biotronik and proctor for Boston Scientific. T.F.

đena. Što se tiče antitrombotske terapije, i dalje ostaje izazov određivanja optimalnog trajanja DAPT-a prema individualnom riziku bolesnika. U konačnici, lošiji ishodi bolesnika s RA-om u usporedbi s onima bez RA-a upućuje na to da ovi prvi zahtijevaju agresivnije liječenje potvrđeno u budućim studijama.

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