Godina 2019. u kardiologiji: akutni koronarni sindrom

The year in cardiology: acute coronary syndromes
The year in cardiology 2019

[iD]Adrian P. Banning[1]*,
Filippo Crea[2],
Thomas F. Lücher[3]

[1]Department of Cardiology, John Radcliffe Hospital and University of Oxford, Oxford, UK

[2]Fondazione Policlinico Univeristario A. Gemelli, Universita` Cattolica del Sacro Cuore, Rome, Italy

[3]Royal Brompton & Harefield Hospital, Imperial College, London, UK

Uvod

U proteklih pet desetljeća dogodili su se veliki napredci u liječenju akutnoga koronarnog sindroma (AKS), osobito uvođenjem defibrilacije, beta-blokatora, trombolitičke terapije, acetilsalicilatne kiseline, primarne perkutane intervencije (PCI, engl. *percutaneous coronary intervention*), P_2Y_{12} inhibitora, statina, radijalnog pristupa te PCSK9 inhibitora.[1] Međutim, unatoč svekolikom napretku u liječenju, postoji akutni rizik od smrtnosti, osobito u bolesnika u kliničkoj slici kardiogenog šoka ili nakon reanimacije, s rastućom učestalošću velikih kardiovaskularnih događaja (MACE, engl. *major adverse cardiovascular event*).[2] Stoga postoji potreba za daljnjim poboljšanjem liječenja AKS-a. Tijekom 2019. godine nekoliko je važnih članaka objavljeno u *European Heart Journalu* i ostalim časopisima koji su produbili naše znanje o spektru AKS-a i njihovu liječenju. U današnje vrijeme bolesnici koji se prezentiraju akutno nastalim bolovima u prsima i promjenama EKG-a ili povišenim vrijednostima biomarkera, mogu imati infarkt miokarda s elevacijom ST-segmenta (STEMI) ili bez elevacije ST-segmenta (NSTE-

Preamble

The management of acute coronary syndromes (ACS) has made enormous progress over the last five decades due to the introduction of defibrillation, beta blockers, thrombolytics, aspirin, primary percutaneous transluminal intervention (PCI), P_2Y_{12} inhibitors, statins, radial access, and eventually PCSK9 inhibitors, among others.[1] However, in spite of all these remedies, there is a remaining acute mortality risk, in particular, in those presenting in cardiogenic shock or after resuscitation and an accruing number of major cardiovascular events (MACE) over the following years.[2] Thus, there is an unmet need in the management of ACS. In 2019, there were a number of important papers published in the *European Heart Journal* and other journals that deepened our knowledge about the spectrum of ACS and their management. Today patients presenting with acute chest pain and changes in the electrocardiogram (ECG) or biomarkers may have ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) caused by atheroma, coronary dissection,[3] takotsubo

MI) čiji uzroci mogu biti aterom, koronarna disekcija[3], Takotsubo sindrom[4,5], MINOCA (engl. *Myocardial infarction with Non-Obstructed Coronary Arteries*)[6] ili miokarditis.[7]

Genetika

Sekvenciranje čitavog genoma i rani akutni infarkt miokarda

Relativna prevalencija i važnost monogenskih mutacija vezanih za porodičnu hiperkolesterolemiju (PH) i puteva visokoga poligenskog zbroja (kumulativni učinak više zajedničkih varijanti) na ranu pojavu infarkta miokarda (IM) nisu razjašnjeni. Sekvenciranje čitavog genoma omogućuje istodobno određivanje monogenskih mutacija i poligenskoga zbroja svakog pojedinca. Khera i sur.[8] sekvencirali su čitavi genom u 2081 bolesnika hospitaliziranih zbog preuranjenog akutnog infarkta miokarda (AIM) kako bi odredili prevalenciju i kliničku važnost mutacija vezanih uz PH i visokoga poligenskog zbroja. Primijetili su PH mutaciju u 1,7 % bolesnika i visoki poligenski zbroj u 17 % bolesnika, pri čemu su obje opservacije bile povezane s trostruko većom vjerojatnošću preuranjenog AIM-a. Uz kliničku stratifikaciju rizika, poligenski zbroj može pridonijeti boljem razumijevanju mehanicističkih temelja AIM-a. Naime, rizik povezan s visokim poligenskim zbrojem nije rezultat diskretnih podležećih mehanizama, nego kvantitativna mješavina brojnih rizičnih čimbenika.

Patofiziologija

Ruptura plaka i procjena cijeljenja prikazani optičkom koherentnom tomografijom

Različiti su mehanizmi i patološki supstrati erozije i fisure plaka. Naime, plakovi komplicirani erozijom uglavnom su bogati matriksom, siromašni lipidima i bez značajnih kolekcija makrofaga, za razliku od plakova koji rupturiraju, koji karakteristično imaju tanku fibroznu kapu, velike lipidne kolekcije te mnoštvo pjenušavih stanica.[9] U prospektivnom istraživanju u 211 bolesnika sa STEMI-ijem, podvrgnutih optičkoj koherentnoj tomografiji (OCT) vodeće lezije prije same intervencije, Tan i sur.[10] našli su kako su razine trimetilamin N-oksida (TMAO), metabolita vezanog za crijevnu mikrobiotu, koji nastaje iz fosfadilkolina i kolina iz hrane, bile znatno i neovisno povišene u bolesnika s fisurom u odnosu prema onima s erozijom plaka. Područje ispod ROC krivulje za razlikovanje rupture i erozije plaka iznosilo je 0,89. Stoga plazmatska razina TMAO može potencijalno služiti kao novi biomarker rupture plaka u bolesnika sa STEMI-ijem te čini prognostički marker kod ovakvih bolesnika. Ovo može biti važno zbog razlike u stratifikaciji rizika i pristupa liječenju između fisure i erozije plaka.

Zacijeljena ruptura plaka ili erozija može se smatrati znakom prekinutog AKS-a. Međutim, uloga cijeljenja plaka u prirodnom tijeku ishemijske bolesti srca (IBS) uglavnom nije poznata. OCT je validirana u detekciji zacijeljenih koronarnih plakova s obzirom na histologiju pa stoga nudi mogućnost procjene njihova kliničkog značenja. *Vergallo i sur.*[11] procjenjivali su cijeljenje plakova u dvjema skupinama bolesnika s potpuno oprečnim kliničkim slikama IBS-a: (**a**) bolesnici s ponavljanim AKS-om, što je definirano kao anamnestički podatak o barem trima AIM-ovima ili najmanje četirima AKS-ovima s barem jednim AIM-om; (**b**) bolesnici s dugotrajnim

syndrome,[4,5] MINOCA (Myocardial infarction with Non-Obstructed Coronary Arteries[6]), or myocarditis.[7]

Genetics

Whole-genome sequencing and early acute myocardial infarction

The relative prevalence and importance of monogenic mutations related to familial hyper-cholesterolaemia (FH) and of high polygenic score (cumulative impact of many common variants) pathways for early-onset myocardial infarction (MI) remain uncertain. Whole-genome sequencing enables simultaneous ascertainment of both monogenic mutations and polygenic score for each individual. Khera *et al.*[8] performed whole-genome sequencing in 2081 patients hospitalized for early-onset AMI to assess the prevalence and clinical importance of FH mutations and a high polygenic score. They observed an FH mutation in 1.7% of patients and a high polygenic score in 17% of patients, each of which was associated with a greater than three-fold increased odds of early-onset AMI. Beyond clinical risk stratification, the polygenic score may additionally foster insights into the mechanistic underpinnings of AMI. Indeed, this risk associated with a high polygenic score is not the result of a discrete underlying mechanism but rather a quantitative blend of numerous risk pathways.

Pathophysiology

Plaque rupture and healing assessed by optical coherence tomography

The mechanisms and the pathologic substrate of plaque erosion and plaque fissure are different. Indeed, plaques complicated by erosion tend to be matrix-rich, lipid-poor, and usually lack prominent macrophage collections, unlike plaques that rupture, which characteristically have thin fibrous caps, large lipid pools, and abundant foam cells.[9] In a prospective study in 211 patients with STEMI who underwent pre-intervention optical coherence tomography (OCT) examination for the culprit lesion, Tan *et al.*[10] found that trimethylamine N-oxide (TMAO) levels, a gut microbiota-dependent metabolite derived from dietary phosphatidylcholine and choline, were significantly and independently higher in patients with plaque fissure than in those with plaque erosion. The area under the receiver operating characteristic curve for distinguishing plaque rupture from plaque erosion was 0.89. Thus, plasma TMAO has the potential to serve as a novel biomarker for plaque rupture in patients with STEMI and indeed is a prognostic marker in these patients (see below). This might be relevant because risk stratification and management are probably different for plaque fissure and erosion.

Healed plaque ruptures or erosions may be considered as a signature of an aborted ACS. However, the role of plaque healing in the natural history of ischaemic heart disease (IHD) is largely unknown. OCT has been validated for the detection of healed coronary plaques against histology and therefore, offers the opportunity of assessing their clinical relevance. Vergallo *et al.*[11] assessed plaque healing in two groups of patients at the extremes of the clinical presentations of IHD: (**a**) patients with recurring ACS, defined as history of at least three AMIs or at least four ACS with at least one AMI; (**b**) patients with long-standing chronic coronary syndromes, defined as a

kroničnim koronarnim sindromima, definiranima kao minimalno 3 godine stabilne angine, bez ranijih AKS-a. U prvoj grupi evaluirane su lezije nevezane za AKS. Nađeno je kako su bolesnici s opetovanim AKS-om imali izrazit aterosklerotski fenotip u usporedbi s bolesnicima s kroničnim koronarnim sindromom i dugotrajnom anginom, uključujući i mnogo nižu prevalenciju zacijeljenih koronarnih plakova, što upućuje na to kako cijeljenje plaka možda ima ulogu u prirodnom tijeku bolesti u bolesnika s IBS-om.

U drugom istraživanju u vezi s OCT-om, Fracassi *i sur.*[12] procjenjivali su cijeljenje plaka u stenozama povezanima s AKS-om i među 376 bolesnika s AKS-om našli su cijeljenje plaka u više od četvrtine. Ti su bolesnici češće imali šećernu bolest ili hiperlipidemiju; nadalje, zacijeljeni plakovi često su imali OCT obilježja lokalne ili sistemske upale. Ovo upućuje na to da kombinacija rizičnih čimbenika i lokalne, uz sistemsku upalu, može nadjačati zaštitne mehanizme cijeljenja plaka i predisponirati te plakove da razviju okluzivne trombe. Stoga bolje poznavanje mehanizama koji potiču cijeljenje plaka može pružiti nove terapijske ciljeve za smanjenje opterećenja AKS-om, uz optimalnu kontrolu rizičnih čimbenika.

Mehanizmi koronarne mikrovaskularne opstrukcije

Brzo otvaranje i postavljanje stenta u okludirane epikardijalne koronarne arterije hitnom PCI donijelo je revoluciju u liječenje bolesnika sa STEMI-jem. Unatoč tehničkim napredcima i uvođenju brojnih antitrombocitnih i antikoagulantnih lijekova, više od trećine bolesnika pokazuje znakove koronarne mikrovaskularne opstrukcije (KMVO) koja umanjuje korist od naizgled uspješne PCI. Mehanizmi KMVO-a i dalje su nepoznati, a prevencija i liječenje ostaju nedostignuta potreba.

Herring *i sur.*[13] zaključili su kako su bolesnici sa STEMI-jem s najvišim vrijednostima neuropeptida Y u koronarnom sinusu imali mnogo nižu koronarnu rezervu protoka i viši indeks mikrovaskularne rezistencije, mjerene žicom za koronarni protok, a oboje su markeri KMVO-a. Nakon dva dana imali su i mnogo više edema miokarda i mikrovaskularne opstrukcije (MVO) na oslikavanju magnetnom rezonancijom (MR) te mnogo nižu ejekcijsku frakciju i više dilatiranu klijetku šest mjeseci poslije. Zanimljivo, neuropeptid Y (NPY) (100 − 250 nM) uzrokovao je značajnu vazokonstrikciju mikrovaskularnih koronarnih arterija u štakora povećanjem kalcijskih valova vaskularnih glatkih mišića te povećanje koronarne vaskularne rezistencije i veličine infarkta u izoliranim srcima prema Langendorffovoj tehnici. Ovakvi su učinci blokirani antagonistima receptora Y1 BIBO3304. Imunohistokemija ljudske koronarne mikrovaskulature potvrdila je prisutnost Y_1-receptora u vaskularnim glatkim mišićima. Stoga bi antagonizam NPY mogao biti budući terapijski cilj u prevenciji KMVO-a (**slika 1**).

Novi uvidi u remodeliranje nakon infarkta miokarda

Imunosni odgovor na AIM uključuje dvije uzastopne faze koje su podjednake važnosti: upalnu i reparatornu fazu. Tijekom upalne faze neutrofili i upalni Ly6C^{hi} monociti skupljaju se u ishemičnom miokardu. Posljedično, Ly6C^{hi} monociti omogućuju nastanak reparatornih Ly6Clo makrofaga, koji imaju važnu ulogu u oporavku srca. Ravnoteža između ovih dviju faza ključna je za oporavak funkcije srca i prognozu bolesnika. Pretjeran upalni odgovor na AIM povećava ozljedu miokarda, što dovodi do većeg infarkta i gubitka funkcije. Unatoč tomu, dosadašnja klinička ispitivanja koja su istraživala uči-

minimum 3-year history of stable angina in the absence of previous ACS. In the first group, non-culprit plaques only were assessed. They found that patients with recurrent ACS had a distinct atherosclerotic phenotype compared with those with chronic coronary syndrome and longstanding angina, including a much lower prevalence of healed coronary plaques, suggesting that plaque healing may play a role in leading the natural history of patients with IHD.

In another OCT study, Fracassi *et al.*[12] assessed plaque healing in the culprit stenosis, among 376 patients with ACS and found plaque healing in more than one-quarter. Such patients more frequently were diabetic or hyperlipidaemic; furthermore, healed plaques frequently showed OCT features of local and systemic inflammation. This suggests that the combination of risk factors and local in addition to systemic inflammation may outweigh the protective mechanism of plaque healing and predispose those plaques to develop occlusive thrombus. Thus, a better knowledge of the mechanisms promoting plaque healing might provide new therapeutic targets to reduce ACS burden in addition to optimal risk factor control.

Mechanisms of coronary microvascular obstruction

The rapid re-opening and stenting of occluded epicardial coronary arteries via emergency PCI have revolutionized STEMI treatment. Despite technical refinements and the introduction of numerous antiplatelet and anticoagulant drugs, more than one-third of patients demonstrate coronary microvascular obstruction (CMVO) which deny the benefit of an apparently successful PCI. The mechanisms of CMVO are still largely unknown, while its prevention and treatment remain an unmet need.

Herring *et al.*[13] found that STEMI patients with the highest neuropeptide Y levels in the coronary sinus had significantly lower coronary flow reserve, and higher index of microvascular resistance measured with a coronary flow wire, both markers of CMVO. After 2 days, they also had significantly higher levels of myocardial oedema and microvascular obstruction (MVO) on magnetic resonance imaging (MRI), and significantly lower ejection fractions and ventricular dilatation 6 months later. Interestingly, neuropeptide Y (NPY) (100−250 nM) caused significant vasoconstriction of rat microvascular coronary arteries via increasing vascular smooth muscle calcium waves, and increased coronary vascular resistance and infarct size in Langendorff hearts. These effects were blocked by the Y1 receptor antagonist BIBO3304. Immunohistochemistry of the human coronary microvasculature confirmed the presence of vascular smooth muscle Y_1 receptors. Thus, antagonism NPY might be an attractive future therapeutic target in the prevention of CMVO (**Figure 1**).

New insight into post-myocardial infarction remodelling

The immune response to AMI involves two equally important, consecutive phases: the inflammatory phase and the reparatory phase. During the inflammatory phase, neutrophils and inflammatory Ly6C^{hi} monocytes are recruited into the ischaemic myocardium. Subsequently, the Ly6C^{hi} monocytes give rise to reparatory Ly6Clo macrophages, with an important role in cardiac recovery. A balance between the two phases is crucial for recovery of cardiac function and patient prognosis. An excessive inflammatory response to AMI amplifies myocardial injury, leading to larger infarcts and loss of
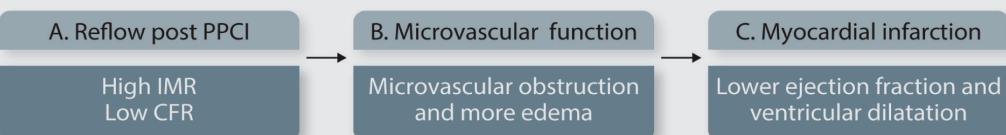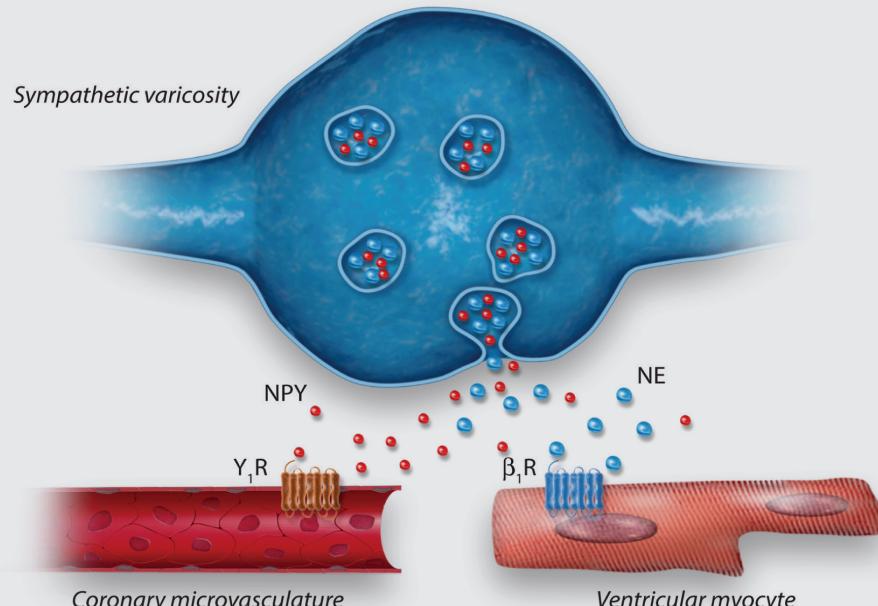
FIGURE 1. Neuropeptide-Y following primary percutaneous coronary intervention for ST-elevation myocardial infarction causes vasoconstriction of the coronary microvasculature and is associated with a high index of microcirculatory resistance and low coronary flow reserve, leading to microvascular obstruction, oedema, and eventually a lower ejection fraction and ventricular dilatation. Redrawn with permission from Ref.[13]

nak protuupalnih strategija u AIM-u nisu pokazala učinkovitost, a katkad su imala i štetan učinak. Učinkovita bi terapija idealno inhibirala štetne učinke pretjeranoga upalnog odgovora a da ne smanjuje učinkovitost mehanizama za oporavak.

Alarmini su skupina heterogenih molekula koje se oslobađaju iz umirućih stanica i aktiviranih leukocita, koji signaliziraju ozljedu tkiva i pokreću prirođen imunosni odgovor. S100A9 i njegov dimerizacijski partner S100A8, također poznati i kao proteini povezani s mijeloidom 8 i 14, proupalni su alarmini koji se proizvode i spremaju u velikim količinama u neutrofilima te se skupljaju na mjestu akutne koronarne okluzije.[14] Marinković i sur.[15] proveli su istraživanje u 524 bolesnika s AKS-om i otkrili kako su visoke plazmatske razine S100A8/A9 u vrijeme AKS-a povezane s nižom ejekcijskom frakcijom lijeve klijetke (LVEF) nakon godinu dana i povećanom učestalošću hospitalizacija zbog zatajivanja srca. Štoviše, u *wild-type* C57BL/6 miševa s AIM-om što ga uzrokuje trajno podvezivanje koronarne arterije, liječenje blokatorom S100A9 ABR-238901 tijekom upalne faze imunosnog odgovora, inhibiralo je proliferaciju hematopoetičnih matičnih stanica i otpuštanje mijeloidnih stanica iz koštane srži. Ovakvo je liječenje smanjilo broj neutrofila i monocita/makrofaga u miokardu, poticalo protuupalno okruženje te znatno popravi-

function. However, clinical trials testing anti-inflammatory strategies in AMI have so far led to non-significant or even deleterious effects. Ideally, an efficient therapy should inhibit the damaging effects of excessive inflammation, while leaving the repair mechanisms intact.

Alarmins are a group of heterogeneous molecules released from dying cells and activated leucocytes that signal tissue damage and trigger an innate immune response. S100A9 and its dimerization partner S100A8, also called myeloid-related proteins 8 and 14, are proinflammatory alarmins that are readily produced and stored in large amounts in neutrophils and are increased at the site of acute coronary occlusion.[14] Marinković *et al.*[15] studied 524 patients with ACS and found that high plasma S100A8/A9 at the time of ACS was associated with lower left ventricular ejection fraction (LVEF) at 1 year and increased hospitalization for heart failure during follow-up. Moreover, in wild-type C57BL/6 mice with AMI induced by permanent coronary artery ligation, treatment with the S100A9 blocker ABR-238901 during the inflammatory phase of the immune response inhibited haematopoietic stem cell proliferation and myeloid cell egression from the bone marrow. The treatment reduced the numbers of neutrophils and monocytes/macrophages in the myocardium, promoted

lo funkciju srca u usporedbi s kontrolnom skupinom. Kako bi se replicirao klinički scenarij, potvrdili su učinak liječenja u mišjem modelu ishemije i reperfuzije. U usporedbi s neliječenim miševima, trodnevno liječenje s ABR-238901 znatno je popravilo LVEF. Stoga blokada S100A9 može činiti potencijalnu strategiju za unaprjeđenje prognoze u bolesnika s AKS-om.

Tang *i sur.*[16] istraživali su učinke crijevne mikrobiote na oporavak srca nakon AIM-a. C57BL/6J miševi tretirani su antibioticima sedam dana prije AIM-a kako bi se uklonila crijevna mikrobiota. Miševi liječeni antibioticima pokazali su mnogo veći stupanj mortaliteta nakon AIM-a, povezan s dozom liječenja, koji se objasnio reorganizacijom crijevne flore, kao što je smanjenje *Lactobacillusa*. Fiziološki status i preživljenje miševa znatno su se poboljšali nakon fekalne rekonstitucije ili prehrambenog nadomještanja masnih kiselina kratkih lanaca, koje su izmijenjene nakon liječenja antibioticima; ova je korist postignuta kroz imunomodulatorne učinke. Nadalje, primjena probiotika s *Lactobacillusom* u miševa liječenih antibiotikom prije AIM-a imalo je kardioprotektivan učinak. Zato ovo istraživanje otkriva negativne učinke antibiotika na preživljenje nakon IM-a te upućuje na obećavajuću terapijsku strategiju, koja uključuje modulaciju sastava crijevne flore s pomoću nadomještanja probioticima (**slika 2**).

an anti-inflammatory environment, and significantly improved cardiac function compared with controls. To mimic the clinical scenario, they further confirmed the effects of the treatment in a mouse model of ischaemia and reperfusion. Compared with untreated mice, 3-day ABR-238901 treatment significantly improved LVEF. Thus, S100A9 blockade might represent a feasible strategy to improve prognosis in ACS patients.

Tang *et al.*[16] investigated the effects of gut microbiota on cardiac repair after AMI. C57BL/6J mice were treated with antibiotics 7 days before AMI to deplete mouse gut microbiota. Antibiotic-treated mice displayed drastic, dose-dependent mortality after AMI associated with a reorganization of the gut microbial community such as a reduction in Lactobacillus. The physiological status and survival of mice were significantly improved after faecal reconstition or dietary supplementation with short-chain fatty acids that are altered after antibiotic treatment; this benefits appeared to be mediated by immunomodulatory effects. In addition, supplementing antibiotic-treated mice with a Lactobacillus probiotic before AMI restored yielded cardioprotective effects. Thus, this study uncovers the adverse effects of antibiotics on survival after MI and addresses a promising therapeutic strategy that involves modulation of gut microbiota composition through probiotic supplementation (**Figure 2**).

FIGURE 2. Please see the original article (Eur Heart J. 2020 Feb 14;41(7):821-832.)

Mehanizimi Takotsubo sindroma

U 55 bolesnika sa Takotsubo sindromom, Scally *i sur.*[17] pronašli su miokardijalne makrofagne upalne infiltrate koristeći se oslikavanjem s pomoću MR-a, kao i promjene distribucije podskupina monocita i porast sistemskih proupalnih citokina. Mnoge od ovih promjena bile su prisutne i nakon pet mjeseci, što upućuje na postojanje stanja kronične upale koja je niskoga stupnja. Očito, trebamo tek razjasniti je li upala uzrok ili posljedica akutnih promjena vezanih za Takotsubo. Također, nejasna je štetnost upale i povezanost s dugoročnim posljedicama ovoga stanja. U svakom slučaju, moguće je da upala ima ulogu u kompleksnoj patogenezi tog sindroma.

Važna nova saznanja uključuju i nalaz funkcionalnog MR-a mozga koji upućuje na to da promijenjeno procesiranje autonomnih limbičnih i centralnih signala imaju ključnu ulogu u Takotsubo sindromu te može objasniti neprimjerenu reakciju simpatičkoga živčanog sustava na stresne podražaje. Stoga možemo naslutiti da je Takotsubo sindrom uzrokovan bolešću mozga, a da je srce ciljni organ.[18]

Mechanisms of takotsubo syndrome

In 55 patients with takotsubo syndrome, Scally *et al.*[17] found myocardial macrophage inflammatory infiltrates as assessed by MRI as well as changes in the distribution of monocyte subsets and an increase in systemic pro-inflammatory cytokines. Many of these changes persisted for at least 5 months suggesting a low-grade chronic inflammatory state. Obviously, whether inflammation is a cause or a consequence of the acute takotsubo event remains to be shown. Moreover, whether inflammation is maladaptive and implicated in the persistence in the long-term consequences of this condition is uncertain. Nevertheless, inflammation might play a role in the complex pathogenesis of this syndrome.

Most importantly, novel investigations using functional MRI of the brain suggest that an altered limbic and central autonomic signal processing plays a crucial role in takotsubo and may explain the inappropriately excessive reaction of the sympathetic nervous system to stressful triggers. Thus, takotsubo is indeed by a brain disease and the heart may just represent the target organ.[18]

Dijagnoza

Troponini

Boeddinghaus *i sur.*[19] prospektivno su uključili bolesnike koji su imali simptome koji su upućivali na AIM u trima velikim dijagnostičkim istraživanjima kako bi se procijenila valjanost 0/1h algoritma ovisno o dobi (<55, ≥55 do <70 i ≥70 godina). Mogućnost algoritma Europskoga kardiološkog društva (ESC) s visokoosjetljivim troponinom (hs-cTNT, engl. *high-sensitivity cardiac troponin T*) da sa sigurnošću isključi AIM bila je vrlo visoka, uz osjetljivost od >99,3 % u svim dobnim skupinama, dok se učinkovitost trijaže smanjivala porastom dobi, uz pad osjetljivosti s 93 % na 55 %. Nešto više isključne koncentracije optimirane za starije bolesnike održale su vrlo visoku isključnu sigurnost i povisile specifičnost. Zaključci su potvrđeni u dvjema validacijskim kohortama te također za visokoosjetljivi troponin I (hs-TnI). Makar je sigurnost ESC-ova 0/1h algoritma ostala vrlo visoka, porastom dobi bolesnika znatno su smanjene ukupna učinkovitost i uključna točnost. Stoga se može razmotriti uporaba nešto viših isključnih koncentracija za starije bolesnike, premda i dalje ostaje problem tumačenja nalaza u slučaju prisutnosti komorbiditeta (poput kronične bubrežne bolesti, kroničnog zatajivanja srca, fibrilacije atrija i dr.) koje također treba uzeti u obzir. Twerenbold *i sur.*[20] potvrdili su izvrsnu primjenjivost, kratko vrijeme potrebno do otpusta iz hitne službe i nisku 30-dnevnu učestalost MACE-a povezanu s rutinskom kliničkom uporabom ESC-ova 0/1h algoritma za zbrinjavanje bolesnika koji dolaze u hitnu službu s akutnim bolovima u prsnom košu.

Napokon, važni koncepti za uvođenje hs-cTn metodologije i preporuke za prethodnu edukaciju razmotreni su na Stručnom panelu kojim su predsjedali, a zatim ga i publicirali Januzzi *i sur.*[21]

Implantabilni srčani sustavi za uzbunjivanje

Simptomi su i dalje pokatad nedovoljno izraženi u AKS-u. U multicentričnom, randomiziranom ispitivanju implantabilnih srčanih monitora koji alarmiraju, 907 visokorizičnih AKS bolesnika s brzoprogresivnim promjenama ST-segmenta tijekom 6 mjeseci randomizirani su u kontrolnu (isključeni alarmi) ili aktivnu skupinu, nakon čega su alarmi uključeni u svih ispitanika.[22] Ispitivanje sigurnosti uređaja pokazalo je odsutnost komplikacija vezanih uz uređaj u 96,7 % ispitanika. Primarni ishod učinkovitosti (kardijalna ili neobjašnjena smrt, novonastali IM s Q-zupcem, vrijeme od detekcije do prezentacije >2 h nakon dokazanog okluzivnog događaja unutar 7 dana) bio je numerički, međutim, ne i statistički niži u bolesnika koji su imali aktivirane alarme. Kada je razdoblje opservacije produljeno na 50, 70 i 90 dana u prespecificiranoj analizi, koja je uključivala većinu potvrđenih okluzivnih događaja u kontrolnoj grupi i eksplorativnu analizu s dvostrukim početnim EKG-om kako bi se smanjile smetnje, primijećeno je znatno smanjenje primarnog ishoda. Također su alarmi znatno skratili vrijeme od detekcije do dolaska u medicinsku ustanovu. Ovaj bi uređaj mogao biti koristan u visokorizičnih bolesnika u identifikaciji asimptomatskih događaja.

Stratifikacija rizika

Biomarkeri

Među 4257 bolesnika u VISTA-16 ispitivanju, početni i kasniji porasti vrijednosti visokoosjetljivog C-reaktivnog proteina

Diagnosis

Troponins

Boeddinghaus *et al.*[19] prospectively enrolled patients presenting with symptoms suggestive of AMI in three large diagnostic studies in order to assess the validity of the 0/h-algorithms according to age (<55 years, ≥55 to <70 years, and ≥70 years). Rule-out safety of the ESC high-sensitivity cardiac troponin T (hs-cTnT) 0/1 h-algorithm was very high with a sensitivity of >99.3% in all age-strata, while triage efficacy decreased with increasing age with sensitivity dropping from 93% to 55%. Slightly higher cut-off concentrations optimized for older patients maintained very high safety of rule-out and increased specificity. Findings were confirmed in two validation cohorts and also for hsTnI. While safety of the ESC 0/1 h-algorithms remained very high, increasing age significantly reduced overall efficacy and the accuracy of rule-in. Thus, alternative slightly higher cut-off concentrations may be considered for older patients, although the problem remains for other confounders like chronic kidney disease, chronic heart failure, atrial fibrillation, and others that also need to be incorporated. Twerenbold *et al.*[20] confirmed the excellent applicability, short time to emergency department discharge, and low rate of 30-day MACE associated with the routine clinical use of the ESC 0/1-h-algorithm for the management of patients presenting with acute chest discomfort to the emergency department in a real-world setting.

Finally, important concepts for institutional transition to hs-cTn methodology providing recommendations useful for education before implementation have been reported in an Expert Panel chaired published by Januzzi *et al.*[21]

Implantable cardiac alert system

Symptoms remain a poor prompt for ACS. In a multicentre, randomized trial of an implantable cardiac monitor that alerted 907 high-risk ACS patients with rapidly progressive ST-segment deviation randomized to a control (alarms deactivated) or treatment group for 6 months, after which alarms were activated in all subjects.[22] Safety revealed a 96.7% freedom from system-related complications. The primary efficacy endpoint of cardiac or unexplained death, new Q-wave MI, and detection to presentation time >2 h following a confirmed occlusive event within 7 days was numerically, but not statistically reduced among patients with activated alarms group. When the observation window was extended to 50, 70, and 90 days in a prespecified analysis to include the majority of confirmed occlusive events in the control group, and an exploratory dual-baseline ECG analysis was used to reduce noise, a significant reduction in the primary endpoint was observed. Moreover, alarms significantly decreased detection to arrival time at a medical facility. This device may be beneficial among high-risk subjects in potentially identifying asymptomatic events.

Risk stratification

Biomarkers

Among 4257 patients of the VISTA-16 trial, initial and subsequent increases in high-sensitivity C-reactive protein (hsCRP) levels during 16 weeks after ACS were associated with a greater risk of the combined MACE endpoint, cardio-

(hsCRP) tijekom 16 tjedana nakon AKS-a bili su povezani s većim rizikom od kombiniranog ishoda MACE-a, kardiovaskularne i smrti svih uzroka, unatoč liječenju prema smjernicama.[23] Bit će potrebno daljnje istraživanje kako bi se odredilo pomažu li inicijalna i serijska mjerenja hsCRP-a u usmjeravanju uporabe ciljane protuupalne terapije nakon AKS-a ili su za to potrebni specifičniji markeri upale.

Četiri nova biomarkera istraživana su u različitim istraživanja u bolesnika s AKS-om: (**a**) galectin-3, impliciran u fibrozi[24]; (**b**) narušena endogena fibrinoliza[25]; (**c**) trimetillizin i TMAO, metabolit crijevne mikrobiote[26]; (**d**) kapacitet za izlučivanje serumskog kolesterola[27]. Svi ti biomarkeri neovisno su povezani s MACE-om tijekom praćenja. Potrebna su daljnja istraživanja kako bi se odredilo identificiraju li skupine bolesnika koji trebaju personalizirano liječenje.

Lindholm i sur.[28] istraživali su povezanost između cystantin-C, faktora diferencijacije rasta-15 (GDF-15), hsCRP, hs-TnT i TnI te N-terminalnog pro-B-tipa natriuretskog peptida (NT-proBNP) i specifičnih uzroka smrti među 17 095 bolesnika s AKS-om u istraživanju PLATO. Zaključili su kako su NT-proBNP i GDF-15 snažno povezani s ukupnom smrtnosti, na temelju povezanosti sa smrću uzrokovanom zatajivanjem srca, aritmijama i iznenadnom srčanom smrću. Faktor diferencijacije rasta-15 imao je najjaču povezanost sa smrću zbog drugih vaskularnih ili nevaskularnih uzroka te, moguće, sa smrću zbog krvarenja. Važnost ovih prognostičkih informacija u usmjeravanju liječenja tek treba utvrditi.

Magnetna rezonancija srca i entropija

Entropija je novi parametar proizašao iz MR-a s kasnom gadolinijem naglašenom fazom (LGE MRI, engl. *late gadolinium enhanced magnetic resonance imaging*) sa svrhom evaluacije nehomogenosti tkiva, neovisno o pragovima intenziteta signala. Androulakis i sur.[29] uključili su 154 uzastopna bolesnika s preboljelim AIM-om koji su bili podvrgnuti LGE MRI-ju prije implantacije kardioverterskih defibrilatora (ICD). Zahvaćenost čitave lijeve klijetke entropijom bila je povezana sa smrtnošću. Nakon prilagodbe za višežilnu koronarnu bolest srca, akutnu revaskularizaciju i ejekcijsku frakciju, entropija ožiljka bila je neovisno povezana s prisutnošću ventrikulskih aritmija. Povezanost između entropije lijeve klijetke i smrtnosti može odražavati neželjeno, ireverzibilno, nehomogeno remodeliranje postinfarktne lijeve klijetke te moguće fatalne aritmije. Daljnja su istraživanja potrebna kako bi se ustanovilo omogućuju li ovi, novi markeri bolju identifikaciju kandidata za ugradnju ICD-a nakon AIM-a.

Liječenje

Tikagrelor i prasugrel bili su uspoređivani u istraživanju ISAR-REACT 5 (**slika 3**).[30] Bolesnici s AKS-om kojima je preporučena intrevencijska strategija bili su randomizirani, a primarni ishod činili su smrt, IM ili moždani udar. U tih bolesnika

vascular (CV) death, and all-cause death despite established background therapies.[23] Further studies will be required to determine whether initial and serial hsCRP measurements can help guide the use of targeted anti-inflammatory therapies after ACS or whether more specific inflammatory markers will be needed to this end.

Four new biomarkers have been investigated in different trials in the setting of ACS: (**a**) galectin-3, implicated in fibrosis[24]; (**b**) impaired endogenous fibrinolysis[25]; (**c**) trimethyllysine and TMAO, gut-microbiota derived metabolite[26]; (**d**) serum cholesterol efflux capacity.[27] All these biomarkers were found to be independently associated with MACE at follow-up. Again, further studies will be required to establish whether these markers identify patient subsets who need personalized forms of treatment.

Finally, Lindholm *et al.*[28] assessed the association between cystatin-C, growth differentiation factor-15 (GDF-15), hsCRP, hs-TnT and TnI, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) and specific causes of mortality among 17 095 ACS patients of the PLATO trial. They found that NT-proBNP and GDF-15 were strong markers associated with all-cause death based on their associations with death due to heart failure as well as due to arrhythmia and sudden cardiac death. Growth differentiation factor-15 had the strongest associations with death due to other vascular or non-vascular causes and possibly with death due to bleeding. It remains to establish how to these important prognostic information can guide treatment.

Cardiac magnetic resonance and entropy

Entropy is a new late gadolinium-enhanced MRI-derived parameter to evaluate tissue inhomogeneity, independent of signal intensity thresholds. Androulakis *et al.*[29] enrolled 154 consecutive post-AMI patients undergoing late gadolinium-enhanced MRI prior to implantable cardioverter-defibrillator (ICD) implantation. When entropy involved the entire left ventricle (LV), this was associated with mortality. After adjusting for multivessel disease, acute revascularization, and ejection fraction, entropy of the scar was independently associated with the presence of ventricular arrhythmias. The association between LV entropy and mortality may reflect adverse and irreversible, inhomogeneous remodelling of the post-infarct LV and/or possibly fatal arrhythmias. Further studies are warranted to establish whether this new marker can allow a better identification of candidates for ICD after AMI.

Treatment

Ticagrelor compared to prasugrel were studied in the ISAR-REACT 5 study (**Figure 3**).[30] Patients with ACS and a proposed interventional strategy were randomized and the primary composite endpoint was death, MI, or stroke. In these patients with or without STEMI, prasugrel therapy was superior

FIGURE 3. Please see the original article (Eur Heart J. 2020 Feb 14;41(7):821-832.)

sa STEMI-jem ili bez njega, liječenje prasugrelom bilo je superiorno tikagreloru, bez razlike u krvarenju. Izgledno je kako će ovi važni usporedni podatci promijeniti kliničku praksu.

Vrijeme liječenja

Optimalno vrijeme primjene dvojne antiagregacijske terapije (DAPT, engl. *dual antiplatelet therapy*) u bolesnika sa STEMI-jem istraživano je u *Švedskom registru koronarografija i intervencija na koronarnim žilama*.[31] Bolesnici su podijeljeni u skupine koje su liječene antagonistima P_2Y_{12} receptora prije i onih liječenih nakon procedure. Od 44 804 uključena bolesnika 58 % liječeno je klopidogrelom, 35 % tikagrelorom, i 5 % prasugrelom. Ranije liječenje nije imalo nikakav učinak na preživljenje, otvorenost arterije povezane s infarktom, trombozu stenta ili krvarenje. Ovi su podatci začuđujući, osobito s obzirom na to da se mogao očekivati potencijalan učinak na ranu trombozu stenta. Postojeće Smjernice[32] preporučuju primjenu antiagregacijske terapije u sali za kateterizaciju srca, što ovi podatci podupiru, makar Abtan i Steg[33] upućuju na to da bi se trebalo nastaviti s primjenom antagonista P_2Y_{12} receptora što ranije u bolesnika s mogućim STEMI-jem te da postoji snažna biološka vjerojatnost koristi, bez izgledne štete.

Zahtijevaju li bolesnici s prolaznom elevacijom ST-segmenta (bolesnici s početnom elevacijom ST-segmenta na EKG-u u kojih kasniji EKG pokazuju potpunu rezoluciju elevacije i nestanak simptoma prije primjene reperfuzijske terapije) hitnu revaskularizaciju istraživano je u istraživanju[34] koje je uključivalo 142 bolesnika randomizirana na hitnu (prosjek 0,3 h) ili odgođenu angiografiju (prosjek 22,7 h). Ishod istraživanja bio je veličina infarkta oslikavanjem s pomoću MR-a na 4. dan. Prikazani su infarkti bili uglavnom mali te nije uočena jasna korist od hitne revaskularizacije, makar su 4/71 bolesnika zahtijevala hitnu intervenciju zbog perzistiranja simptoma i elevacije ST-segmenta tijekom čekanja. Posljedično, iz ovih rezultata možemo zaključiti kako se odluka o vremenu revaskularizacije bolesnika s prolaznom ST-elevacijom može temeljiti na dostupnosti koronarografije i pažljivoj kliničkoj procjeni.

Liječenje lezija koje nisu uzrokom IM-a u bolesnika sa STEMI-jem bilo je opširno razmatrano tijekom prošlih godina. Manja su randomizirana ispitivanja upozorila na vjerojatnu korist od potpune revaskularizacije. Veliko istraživanje COMPLETE randomiziralo je 4041 bolesnika sa STEMI-jem (**slika 4**) na potpunu i djelomičnu revaskularizaciju.[35] Potpuna revaskularizacija bila je superiorna pred revaskularizacijom isključivo promjena na krvnoj žili koja je uzrokom IM-a, na temelju smanjenja rizika od kardiovaskularne smrti ili AIM-a. Korist od potpune revaskularizacije bila je prisutna i u smanjenju ishemijskih ishoda. Vrijeme intervencije bilo je manje važno te je odgađanje sekundarne revaskularizacije bilo sigurno. Stoga će korist od potpune revaskularizacije vjerojatno biti odražena u sljedećim smjernicama.

to ticagrelor with no difference in bleeding. These important comparative data are likely to change clinical practice.

Timing of treatment

The optimal timing of administration of dual antiplatelet therapy (DAPT) in STEMI patients was investigated by the *Swedish Coronary Angiography and Angioplasty Registry*.[31] Patients were stratified between either post- or pre-procedure treatment with P_2Y_{12} receptor antagonists. Of the 44'804 patients 58% had been on clopidogrel, 35% on ticagrelor, and 5% on prasugrel. There was no survival benefit from pre-treatment or any impact on infarct-related artery patency, stent thrombosis, or bleeding. These data are surprising as a potential impact on early stent thrombosis, in particular, might have been anticipated. Existing Guidelines[32] recommend catheter-lab administration of antiplatelet drugs and these data are supportive of that strategy, although Abtan and Steg[33] argue that we should continue to give P_2Y_{12} receptor antagonists as early as possible in probable STEMI patients as there is a strong biological plausibility of likely benefit with no obvious likely detriment.

Whether patients with patients with transient ST-elevation (patients who present initially with ST-elevation on the electrocardiogram but, subsequently, show complete normalization of the ST-segment and relief of symptoms before reperfusion therapy) require immediate revascularization was studied in a trial[34] of 142 patients who were randomized to immediate (mean 0.3 h) or delayed angiography (mean 22.7 h). The outcome was infarct size by MRI at Day 4. The observed infarcts were generally small and there was no clear benefit from the immediate strategy, although 4/71 patients required urgent intervention because of further symptoms and ST elevation whilst waiting. Consequently, these data can probably be interpreted as allowing decisions about timing of revascularization in patients with transient STEMI, to be guided by the availability of angiography and careful clinical assessment.

The management of non-culprit lesions in STEMI patients has been extensively discussed over the last years. Small randomized trials have suggested a probable benefit from complete revascularization. The large COMPLETE trial randomized 4041 STEMI patients (**Figure 4**) to complete or partial revascularization.[35] Complete revascularization was superior to culprit-only as it reduced the risk of CV death or AMI. There was also benefit from complete revascularization in reducing ischaemic endpoints. Timing appeared to be less important and deferring any secondary revascularization procedure was safe. Thus, the advantage of complete revascularization will presumably be reflected in subsequent ESC Guidelines.

FIGURE 4. Please see the original article (Eur Heart J. 2020 Feb 14;41(7):821-832.)

Možemo li prilagođivati liječenje u akutnome koronarnom sindromu?

Postoji želja da se medikamentna terapija prilagodi pojedinom bolesniku te, po mogućnosti, pojedinoj leziji. Ovakva bi strategija dopuštala farmakološku optimizaciju zaštite s minimiziranjem nuspojava ili rizika od krvarenja. Rezultati istraživanja CHAMPION PHOENIX[36] upućuju na potrebu karakterizacije kompleksnih koronarnih lezija te pokazuje kako nedovoljno liječenje visokorizičnih lezija rezultira ponovnim revaskularizacijama ili kliničkim događajima. U usporedbi s klopidogrelom u dozi zasićenja, kangrelor je smanjio MACE unutar 48 h nakon PCI-ja u bolesnika s AKS-om bez obzira na početnu kompleksnost lezije. Međutim, apsolutna korist: profil rizika za kangrelor bio je najveći tijekom PCI-ja u kompleksnoj koronarnoj anatomiji. U podistraživanju studije PROSPECT[37] virtualna histologija i intravaskularni ultrazvuk (IVUS) u sivoj skali predviđali su suboptimalni završni angiografski rezultat, što se odražavalo kao visok rezidualni rezultat na Syntax ljestvici nakon intervencije. Detaljan pregledni konsenzus stručnjaka pruža detalje o karakterizaciji akutne koronarne lezije primjenom IVUS-a ili OCT-a te upozorava na potrebu trijaže tijekom terapijskog pristupa.[38]

Nažalost, mjerenje individualnog odgovora na antiagregacijsku terapiju nije pokazalo kliničku korist. Randomiziranje bolesnika na mjerenje funkcije trombocita u istraživanju TROPICAL[39] nije pokazalo mjerljivu kliničku korist. U ovom ispitivanju bolesnici s maksimalnom inhibicijom trombocita bili su najskloniji krvarenju.

Optimizacija liječenja kod infarkta miokarda s elevacijom ST-segmenta

Oko trećine bolesnika sa STEMI-jem ima suboptimalnu reperfuziju nakon PCI-ja i upravo kod njih mogu nastupiti zatajivanje srca i preuranjena smrt. Oslikavanje MR-a može pružiti dokaze MVO-a i miokardijalnog krvarenja.[40] U istraživanju DANAMI-3 odgođena prezentacija[41], definirana kao produljeno vrijeme od ulaska u bolnicu do reperfuzije (engl. *door-to-wire time*), predviđala je neželjene kliničke ishode, sukladno ranijim opservacijama temeljenima na intrakoronarnim fiziološkim mjerenjima koja su upućivala na povišen rizik u bolesnika koji dolaze kasnije.[42] Potrebne su naglašene i kontinuirane kampanje javnog informiranja kako bi se optimirali ishodi u visokorizičnih bolesnika sa STEMI-jem, uz nove, dodatne terapijske mogućnosti. U ovom kontekstu, puna doza intrakoronarno primijenjene tenekteplaze bila je inferiorna pred abciksimabom u malom randomiziranom istraživanju[43], a intrakoronarna primjena niske doze tenekteplaze nakon reperfuzije u ispitivanju T-time također nije smanjila MVO mjerenu oslikavanjem s pomoću MRI-ja.[44]

Rezultate koji potiču generiranje hipoteza prezentirali su istraživači studije MRUSMI (*Microvascular Reperfusion Utilizing Sonothrombolysis in Acute Myocardial Infarction*).[45] Oni su bolesnike sa STEMI-jem randomizirali na standardnu PCI ili intervenciju vođenu dijagnostičkom ultrazvučnom sondom, uz impulse visokog mehaničkog indeksa tijekom infuzije ultrazvučnoga sredstva prije i tijekom PCI-ja. Ultrazvučni impulsi visokog mehaničkog indeksa stvaraju kavitaciju mikromjehurićima koji uzrokuju sile smicanja (*shear forces*), dizajnirane tako da bi otapale intrakoronarne trombe. Kohorta s dodatnom intervencijom imala je višu učestalost rekanalizacije (48 % prema 20 %) i TIMI 3 protoka (32 % prema 14 %) unu-

Can we tailor treatment in acute coronary syndromes?

There remains a desire to tailor drug therapy to the individual patients and perhaps the individual lesion. This strategy would allow pharmaceutical optimization of protection with minimization of side effects or bleeding risk. The CHAMPION PHOENIX trial[36] has suggested that complex coronary lesions can be characterized and that it is inadequate treatment of these 'high risk' lesions that leads to repeat revascularization or clinical events. Compared with a loading dose of clopidogrel, cangrelor reduced MACE occurring within 48 h after PCI in patients with ACS regardless of baseline lesion complexity. However, the absolute benefit: risk profile for cangrelor was greatest during PCI in complex coronary anatomy. In a substudy of the PROSPECT trial,[37] virtual histology and grey scale intravascular ultrasound (IVUS) was a predictor of a suboptimal final angiographic result reflected as a high residual Syntax Score after intervention. A detailed Expert consensus review has provided detail on characterization of acute coronary lesions using IVUS or OCT and suggested a triaged therapeutic approach.[38]

Unfortunately measuring individuals' responses to antiplatelet drugs has not shown clinical utility. Randomizing patients to measuring platelet function in the TROPICAL trial[39] showed no measurable clinical advantage. Within the trial, those patients with maximal platelet inhibition were predictably most prone to bleeding.

Optimizing treatment in ST-segment elevation myocardial infarction

About one-third of STEMI patients have suboptimal reperfusion after PCI and it is this group of patients that might experience heart failure and premature death. MRI can provide evidence of MVO and myocardial haemorrhage.[40] In the DANAMI-3 trial delayed presentation[41] as evidenced by prolonged *door-to-wire-time* predicted adverse clinical outcome, consistent with previous observations using intracoronary physiology measurements suggesting increased risk in these 'late presenters'.[42] Enhanced and continued public information campaigns are required to optimize outcomes in high-risk STEMI patients along with novel adjunctive therapies. In this context, full dose intracoronary tenecteplase was inferior to abciximab in a small randomized trial[43] and using low dose intracoronary tenecteplase after reperfusion in the T-time trial also failed to reduce MVO measured using cardiac magnetic resonance imaging (CMRI).[44]

Hypothesis generating results were presented by the Microvascular Reperfusion Utilizing Sonothrombolysis in Acute Myocardial Infarction (MRUSMI) investigators.[45] They randomized STEMI patients to either standard PCI or diagnostic ultrasound transducer guided, high mechanical index impulses during an ultrasound agent transfusion prior to and following PCI. The ultrasounds high mechanical index impulses create microbubble cavitation that induce shear forces, designed to dissolve intracoronary thrombi. The treatment cohort demonstrated higher recanalization (48% vs. 20%) and TIMI 3 flow rates (32% vs. 14%) within the infarcted vessel ST-segment resolution prior to primary PCI occurred more frequently. Furthermore, infarct size as assessed by MRI and TNT peak values was also reduced by the intervention. Optimizing reperfusion for patients with STEMI when there is lot of thrombus is challenging and these preliminary results hint at a possible alternate approach.

tar infarcirane arterije uz češću rezoluciju ST-segmenta prije primarne PCI. Nadalje, veličina infarkta procijenjena oslikavanjem s pomoću MRI-ja i vršne vrijednosti TnT-a također je bila manja u skupini s dodatnom intervencijom. Optimizacija reperfuzije za bolesnike sa STEMI-jem s velikom količinom tromba zahtjevna je i ovi preliminarni rezultati upućuju na mogući alternativni pristup.

Udaljeno prekondicioniranje u STEMI-ju istraživano je u studiji CONDI-2/ERIC PPCI[46] u kojoj je randomiziran 5401 bolesnik na standarno liječenje (uključujući i placebom udaljeno ishemijsko kondicioniranje u centrima u Velikoj Britaniji) ili udaljeno ishemijsko kondicioniranje (naizmjenična ishemija i reperfuzija primijenjena na ruku kroz četiri ciklusa 5-minutnih inflacija i 5-minutnih deflacija automatizirane manšete) prije primarne PCI. Nažalost, udaljeno ishemijsko kondicioniranje nije poboljšalo kliničke ishode (kardijalna smrtnost ili hospitalizacija zbog zatajivanja srca) nakon 12 mjeseci. Novi pristupi i terapije u ovom su području opravdani ako ovaj eksperimentalno dobro dokumentiran koncept dođe do kliničke primjenjivosti.

Ishodi

Kvaliteta liječenja i ishodi

U kohorti od 389 507 bolesnika s NSTEMI-jem optimalno liječenje definirano kao primjena svih dostupnih terapijskih metoda bilo je obrnuto proporcionalno rizičnom statusu (definiranom s pomoću zbroja na GRACE bodovnoj ljestvici), tj. 25,6 % u niskorizičnih, 18,6 % u umjerenog rizika te 11,5 % u visokorizičnih bolesnika. Nakon 2,3 godine praćenja, povezanost između primjene sve dostupne terapije preporučene smjernicama i poboljšanih ishoda ostala je značajna samo za visokorizične bolesnike s NSTEMI-jem[47]. Stoga je optimalna primjena liječenja preporučena smjernicama za bolesnike s NSTEMI-jem bila povezana s većim preživljenjem u skupini s rastućim rizikom prema GRACE bodovnoj ljestvici, ali se primjena optimalnog liječenja smanjivala porastom rizika, što čini prostor za unaprjeđenje.

Prema rezultatima iz SWEDEHEART registra, ishodi bolesnika s NSTEMI-jem praćenih tijekom 20 godina upućuju na znatno poboljšanje u dugoročnom preživljenju i smanjenje rizika od pojave MACE-a.[48] Ova su poboljšanja bila povezana s postupnim uključivanjem i širokom primjenom PCI-ja te dugoročnom primjenom terapije temeljene na dokazima, što je sukladno učinkovitosti primjene koju opisuju smjernice (**slika 5**).

Korist od programa kardiološke rehabilitacije bila je uspoređena u 839 bolesnika koji su pohađali planirane programe poslije otpusta nakon AKS-a ili kirurške revaskularizacije, dok je 441 bolesnik otpušten bez rehabilitacije.[49] U multivarijatnoj analizi Cox proporcionalnog rizika, program kardijalne rehabilitacije bio je neovisni prediktor niže pojavnosti MACE-a (omjer rizika 0,55), dok su u uparenoj (*propensity mathced*) analizi bolesnici koji su sudjelovali u programu kardijalne rehabilitacije imali i niži ukupni mortalitet (10 % prema 19 %) i kardiovaskularni mortalitet (2 % prema 7 %) u usporedbi s onima koji nisu bili uključeni u program rehabilitacije. Stoga su učinci ambulantne kardijalne rehabilitacije uočljivi i u stvarnome svijetu.

I zaključno, u kohortnom istraživanju sa 123 780 uzastopnih PCI-ja iz *Pan-London PCI Registry* uspoređivani su rezultati u Velikoj Britaniji prije i nakon uvođenja javnog priopćivanja

Remote preconditioning in STEMI was studied in the CONDI-2/ERIC PPCI trial[46] which randomized 5401 patients to standard treatment (including a sham simulated remote ischaemic conditioning at UK sites) or remote ischaemic conditioning (intermittent ischaemia and reperfusion applied to the arm through four cycles of 5-min inflation and 5-min deflation of an automated cuff device) before primary PCI. Unfortunately, remote ischaemic conditioning did not improve clinical outcomes (cardiac death or hospitalization for heart failure) at 12 months. New approaches and therapies within this area are warranted if this experimentally well-documented concept should ever reach the clinical applicability.

Outcomes

Quality of treatment and outcomes

In a cohort of 389 507 NSTEMI patients, optimal care, defined as the receipt of all eligible treatments, was inversely related to risk status (defined by the GRACE risk score), i.e. 25.6% in low, 18.6% in intermediate, and 11.5% in high-risk patients. At the end of 2.3 years of follow-up, the association between the use of all eligible guideline-indicated treatments and improved survival remained only significant for high-risk NSTEMI.[47] Thus, optimal use of guideline-indicated care for NSTEMI was associated with greater survival gains with increasing GRACE risk, but its use paradoxically decreased with increasing GRACE risk, thus leaving room for improvement.

In the SWEDEHEART registry, outcomes of patients presenting with NSTEMI followed over 20 years demonstrated a substantial improvement in long-term survival and reduction in the risk of MACE.[48] These improvements were associated with the gradual uptake and widespread use of PCI and long-term use of evidence-based medications, consistent with the anticipated effectiveness of their implementation as proposed in guidelines (**Figure 5**).

The value of a cardiac rehabilitation programme was compared in 839 patients who attended a planned programme at discharge after ACS or surgical revascularization, while 441 patients were discharged without it.[49] At multivariable Cox proportional hazard analysis, the cardiac rehabilitation programme was an independent predictor of lower occurrence of MACE (hazard ratio 0.55), while in a propensity-matched analysis patients attending the cardiac rehabilitation programme also experienced a lower total mortality (10% vs. 19%) and CV mortality (2% vs. 7%) compared to non-rehabilitated ones. Thus, the positive effects of ambulatory of cardiac rehabilitation are also notable in a real-world population.

Finally, in a cohort study of 123 780 consecutive PCIs from the Pan-London PCI Registry the outcomes pre- and post-public reporting in the UK were compared.[50] After public reporting was introduced, patients were older and had more complex medical problems, while in-hospital MACE and MACCE and 30-day mortality rates were significantly lower. These results probably reflect continued improvements in PCI outcomes concomitant with the introduction of public reporting, but the lower reported complication rate could also reflect a change in the documentation of risk factors and a change in operator behaviour. Reassuring, additional data from the UK
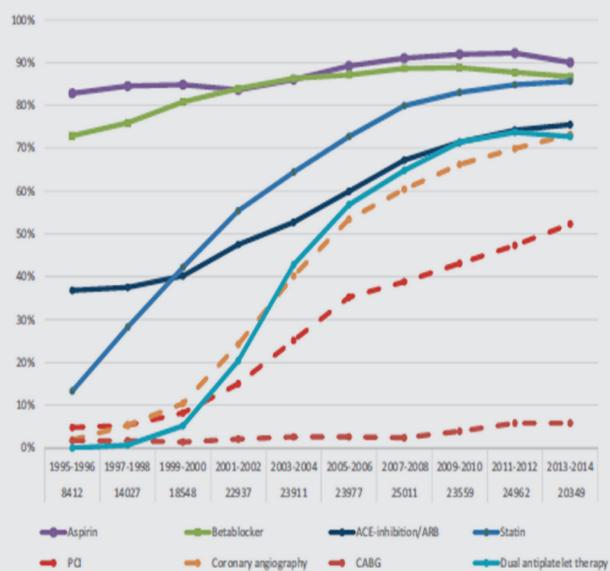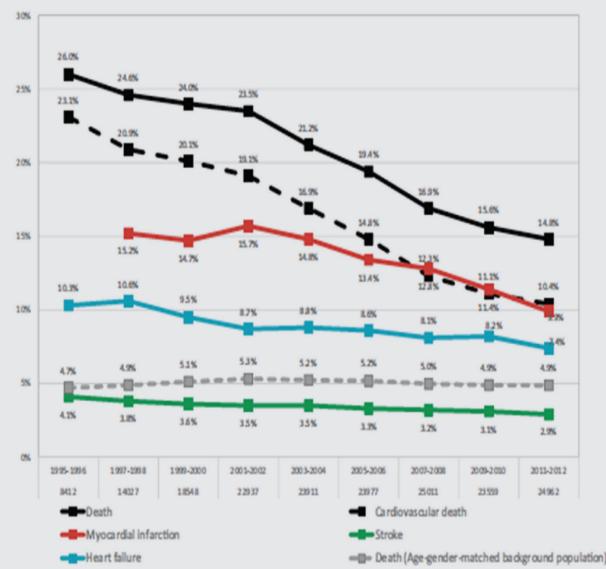
FIGURE 5. **(A and B) Kaplan–Meier estimates of the cumulative incidence of the first coprimary outcome (death from cardiovascular causes or new myocardial infarction) and the second coprimary outcome (death from cardiovascular causes, new myocardial infarction, or ischaemia-driven revascularization), respectively. Insets show the same data on an enlarged y axis.** PCI, percutaneous coronary intervention. Reprinted with permission from Ref.[48]

ishoda.[50] Nakon uvođenja javnog priopćivanja bolesnici su bili stariji i imali kompleksnije medicinske probleme, dok su intrahospitalni MACE i MACCE te 30-dnevna stopa mortaliteta bili mnogo niži. Ovi rezultati vjerojatno odražavaju kontinuirane napretke u ishodima PCI-ja istodobne s uvođenjem mjera javnog priopćivanja, no niža stopa komplikacija mogla bi biti odraz promjene načina dokumentiranja rizičnih čimbenika i promjene u ponašanju operatera. Ohrabrujući su dodatni podatci iz ovog registra koji potvrđuju kontinuirano poboljšavanje ishoda u AKS-u i ne pokazuju razliku u ishodima ovisno o dobu dana kad je liječenje provedeno. Bolesnici liječeni kako hitni u noćnim satima imali su slične ishode kao oni liječeni u radno vrijeme.

Uzroci smrti nakon infarkta miokarda bez elevacije ST-segmenta

U 66 252 bolesnika s NSTEMI-jem koji su bili uključeni u 14 istraživanja TIMI ispitivani su osnovna obilježja, načini i vrijeme smrti. Od 2606 bolesnika u kojih je poznat način smrti, 75,1 % smrti bilo je povezano s MACE-om, 3,0 % s krvarenjem (uključujući intrakranijalno krvarenje), a 21,8 % bilo je vezano uz nekardiovaskularne/nekrvareće događaje.[51] Najčešći način KV smrti bila je iznenadna smrt i ponovljeni AIM (36,4 % i 23,4 %). Učestalost KV smrti povezanih s ponovljenim AIM-om bila je viša u prvih 30 dana nego nakon 30 dana nakon NSTEMI-ja (30,6 % prema 18,7 %), dok je udio iznenadnih smrti bio niži u prvih 30 dana, nego nakon 30 dana (21,6 % prema 46,2 %). Stoga je iznenadna smrt činila najveći udio KV smrti nakon 30 dana. Daljnje istraživanje usmjereno na definiranje

registry also confirm continued temporal improvement in outcomes in ACS and notably demonstrate no difference in outcome depending on the times of day that treatment occurred. Patients treated as emergencies at night had similar outcomes to those treated within 'office hours'.

Modes of death after non-ST-segment elevation myocardial infarction

In 66 252 patients with NSTEMI enrolled in 14 TIMI trials, baseline characteristics and modes and timing of death were examined. Of the 2606 patients with known modes of death, 75.1% were r elated to MACE, 3.0% were related to a bleeding event (including intracranial haemorrhage), and 21.8% were related to a non-CV/non-bleeding event.[51] The most common modes of CV death were sudden death and recurrent AMI (36.4% and 23.4%, respectively). The proportion of CV deaths related to recurrent AMI was higher in the first 30 days than it was after 30 days following NSTEMI (30.6% vs. 18.7%), whereas the proportion of sudden death was lower in the first 30 days than after 30 days (21.6% vs. 46.2%). Thus, sudden death represented the largest proportion of CV deaths after 30 days. Further investigations aimed at defining management approaches to reduce sudden death following NSTEMI may be critical to reducing late mortality.

Outcomes of in-hospital acute coronary syndromes

In a cohort study of 1.3 million patients hospitalized in US Veterans Health Administration facilities, an incidence of

terapijskih pristupa sa svrhom smanjenja učestalosti iznenadne smrti nakon NSTEMI-ja moglo bi biti kritično za smanjenje kasnog mortaliteta.

Ishodi akutnih koronarnih sindroma nastalih u bolnici

U kohortnom istraživanju na 1,3 milijuna bolesnika hospitaliziranih u ustanovama *US Veterans Health Administration* objavljena je incidencija AIM-a nastalih u bolnici od 4,27 na 1000 prijema. Rizični čimbenici povezani s AIM-om nastalim u bolnici jesu anamnestički podatci o IBS-u, povišena frekvencija srca, niska razina hemoglobina te povišena razina leukocita.[52] U usporedbi s uparenim kontrolama, mortalitet je bio mnogo veći u bolesnika s bolničkim AIM-om. Zaključno, bolnički su AIM-ovi česti i povezani s prisutnim kardiovaskularnim čimbenicima rizika i pokazateljima akutne bolesti i imaju visok mortalitet – do 60 % nakon 1 godine. Daljnja istraživanja bolničkih infarkta može pridonijeti smanjenju rizika i poboljšati ishode bolesnika.

Ishodi atipičnih akutnih koronarnih sindroma

Spontana disekcija koronarnih arterija

Spontana disekcija koronarne arterije (SDKA) nedovoljno je dijagnosticirano i slabo razjašnjeno stanje te važan uzrok AIM-a u mladih žena.[3] Kanadska multicentrična, prospektivna, opservacijska studija na 750 bolesnika, čija su predisponirajuća stanja uključivala fibromuskularnu displaziju u 31,1 % slučajeva, sistemsku upalnu bolest u 4,7 %, babinje u 4,5 % te bolesti vezivnog tkiva u 3,6 %.[53] Većina je liječena konzervativno, dok je 14 % podvrgnuto PCI-ju, a tek nekolicina kirurškome koronarnom premoštenju. Bolnički MACE iznosili su 8,8 %, a viši su bili u SDKA-u u razdoblju babinja (20,6 % prema 8,2 %). Ukupni 30-dnevni MACE iznosili su 8,8 %, uz napomenu da su SDKA u babinju i bolesti vezivnoga tkiva bili neovisni prediktori 30-dnevnih MACE-a.

Takotsubo sindrom

U dvama različitim istraživanjima na podatcima iz *InterTak Registry* koja su uključivala više od 1500 bolesnika sa Takotsubo sindromom zaključeno je da su unutarbolnički srčani arest (4,9 % bolesnika)[54] ili prisutnost pridružene maligne bolesti (16,6 % bolesnika)[55] bili povezani s lošijim dugoročnim ishodima. Valja naglasiti da su bolesnici sa srčanim arestom češće bili mlađi, muškarci, imali apikalni takotsubo, fibrilaciju atrija, neurološke komorbiditete, fizičke pokretače, dulji korigirani QT-interval te nižu LVEF, dok su oni sa zloćudnim bolestima bili stariji i vjerojatnije su imali fizičke pokretače, a manje vjerojatno emocionalne.

Infarkt miokarda s neopstruiranim koronarnim arterijama (MINOCA)

Dugoročni ishodi MINOCA bili su istraživani u velikom US Registru u koji je uključeno 286 780 bolesnika s AIM-om, od kojih je 5,9 % imalo MINOCA.[56] Nakon prilagodbe rizika, bolesnici s MINOCA imali su 43 % niži rizik od MACE-a tijekom 12 mjeseci u usporedbi s onima koji su imali AIM i koronarnu bolest srca. Ovaj je obrazac bio sličan i prilagođenim rizicima od komponenti MACE-a. Zaključno, MINOCA ima nepovoljnu prognozu u starijih bolesnika, pri čemu 1 od 5 oboljelih doživi veliki neželjeni događaj u razdoblju od 12 mjeseci.

Žene prema muškarcima

Utjecaj spola istraživan je u 13 451 bolesnika s NSTEMI-jem i STEMI-jem liječenih s pomoću PCI-ja u *Victorian Cardiac*

in-hospital AMI of 4.27 per 1000 admissions and risk factors associated with in-hospital AMI such as history of IHD, elevated heart rate, low haemoglobin level, and elevated white blood cell count were reported.[52] Compared with matched controls, mortality was significantly higher for in-hospital AMI. Thus, in-hospital AMI is common and associated with common CV risk factors and markers of acute illness and with high mortality approaching 60% at 1 year. Further studies of in-hospital AMI may yield opportunities to reduce in-hospital AMI risk and improve patient outcomes.

Outcomes of atypical acute coronary syndromes

Spontaneous coronary artery dissection

Spontaneous coronary artery dissection (SCAD) is an underdiagnosed and poorly understood condition and an important cause of AMI in young women.[3] In the Canadian multicentre, prospective, observational study of 750 patients, predisposing conditions included fibromuscular dysplasia in 31.1%, systemic inflammatory diseases in 4.7%, peripartum in 4.5%, and connective tissue disorders in 3.6% were noted.[53] Most were treated conservatively, while 14% underwent PCI and a few coronary artery bypass surgery. In-hospital composite MACE was 8.8%, but higher in peripartum SCAD (20.6% vs. 8.2%). Overall 30-day MACE was 8.8% with peripartum SCAD and connective tissue disease being independent predictors of 30-day MACE.

Takotsubo syndrome

Two different studies of the *InterTak Registry* including over 1500 patients with takotsubo syndrome found that both in-hospital cardiac arrest (4.9 of patients)[54] or the presence of an associated malignancy (16.6% of patients)[55] were associated with worse long-term outcome. Of note, patients with cardiac arrest were more likely to be younger, male, and have apical takotsubo, atrial fibrillation, neurologic comorbidities, physical triggers, longer corrected QT-interval, and lower LVEF, while those with malignancy were older and more likely to have physical triggers, but less likely to have emotional triggers.

Myocardial infarction with non-obstructed coronary arteries

The long-term outcome of MINOCA was investigated in a large US Registry of 286 780 AMI admissions of which 5.9% had MINOCA.[56] Following risk-adjustment, MINOCA patients had a 43% lower risk of MACE over 12 months compared to those with AMI and coronary artery disease. This pattern was similar for adjusted risks of the MACE components. Thus, MINOCA has an unfavourable prognosis in elderly patients with one in five suffering a major adverse event over 12 months.

Women vs. men

The impact of gender was assessed in 13 451 NSTEMI and STEMI patients undergoing PCI in the *Victorian Cardiac Outcomes Registry* in Australia.[57] Women with STEMI had significant delays in presentation and revascularization with a higher 30-day mortality compared with men, while women with NSTEMI had no delay in presentation or revascularization, with mortality comparable to men. Thus, public awareness campaigns might be needed to address women's recognition and early action for STEMI.

In a Swiss population of 4360 patients with STEMI ischaemic time in women remained greater than that in men due

Outcomes Registry iz Australije.[57] Žene sa STEMI-jem imale su znatnu odgodu u prezentaciji i revaskularizaciji, s višim 30-dnevnim mortalitetom u usporedbi s muškarcima, dok žene s NSTEMI-jem nisu imale odgođenu prezentaciju ili revaskularizaciju, s mortalitetom usporedivim s onim u muškaraca. Zaključno, kampanje sa svrhom podizanja svijesti javnosti mogle bi biti potrebne za naglašavanje važnosti prepoznavanja i ranog reagiranja na simptome STEMI-ja kod žena.

U švicarskoj populaciji od 4360 bolesnika sa STEMI-jem vrijeme ishemije u žena ostalo je veće nego u muškaraca zbog perzistentno duljega vremena do prezentacije bolesnica.[58] U usporedbi s muškarcima, klinički znakovi poput nelagode u prsima nisu predviđali odgodu u prezentaciji žena, što navodi kako su bolesnice sa STEMI-jem rjeđe svoje tegobe pripisivale stanju koje zahtijeva hitno liječenje.

U kineskoj populaciji među 82 196 bolesnika, žene hospitalizirane zbog AKS-a rjeđe su primile akutno liječenje i strategije sekundarne prevencije, nego muškarci.[59] Primijećene razlike prema spolu u intrahospitalnoj smrtnosti bile su uglavnom zbog lošijih kliničkih profila i rjeđe primjene akutnog liječenja temeljenog na dokazima.

Zaključno, Vincent *i sur.*[60] u španjolskoj populaciji osamdesetogodišnjaka u šestomjesečnom praćenju među 535 bolesnika sa STEMI-jem utvrdili su da je ženski spol neovisno povezan sa smrću i hospitalizacijom.

Korisnici javnog zdravstva prema korisnicima privatnoga zdravstvenog osiguranja

U 42 645 i 171 545 bolesnika sa STEMI-jem koji su bili osigurani preko javnoga zdravstva (*Medicaid*) ili privatnoga zdravstvenog osiguranja[61] neprilagođenom je analizom zaključeno kako su korisnici javnoga zdravstva imali nižu učestalost koronarnih revaskularizacija te veću stopu intrahospitalne smrtnosti u usporedbi s privatno osiguranim bolesnicima. Slični su rezultati dobiveni i u uparenim kohortama (*propensity matched cohorts*). Daljnje je istraživanje potrebno kako bi se identificirali i razumjeli uzroci ovih razlika u ishodima ovisno o vrsti osiguranja.

Crnci prema bijelcima

U američkoj kohorti od 6402 bolesnika samoidentificirani bijeli i crni bolesnici razlikovali su se u nekoliko kliničkih i socioekonomskih obilježja.[62] Viša prevalencija obilježja povezanih s crnom rasom korelirala je s višom stopom petogodišnjeg mortaliteta, no nisu primijećene razlike između bolesnika sa sličnim obilježjima koje bi ovisile o rasi. Stoga je veća prevalencija obilježja povezanih s crnom rasom, ali ne i rasa sama, bila vezana s višim rizikom od mortaliteta nakon AIM-a.

Zaključak

Važni podatci iz velikih randomiziranih istraživanja povećali su mogućnosti zbrinjavanja bolesnika s AKS-om. Ističemo kako se prepoznavanje kliničkoga spektra AKS-a povećalo u posljednjim godinama te se atipični oblici, osim klasičnih STEMI-ja i NSTEMI-ja, poput Takotsubo sindroma, disekcije koronarnih arterija, MINOCA i miokarditisa (**slika 6**), pojačano prepoznaju, karakteriziraju, a njihovi uzroci i mehanizmi definiraju. Liječenje ovih, novih oblika AKS-a još nije teme-

to persistently greater patient delays.[58] In contrast to men, clinical signs of ongoing chest discomfort did not predict delays in women, suggesting that female STEMI patients were less likely to attribute symptoms to a condition requiring urgent treatment.

In a Chinese population of 82 196 patients women hospitalized for ACS less frequently received acute treatments and strategies for secondary prevention than men.[59] The observed sex differences in in-hospital mortality were mainly due to worse clinical profiles and fewer evidence-based acute treatments provided to women with ACS.

Finally, Vicent *et al.*[60] in an octogenarian Spanish population of 535 patients with STEMI found that female sex was independently associated with death and hospitalization at 6-month follow-up.

Medicaid beneficiaries vs. privately insured individuals

In 42 645 and 171 545 STEMIs receiving Medicaid or private insurance, respectively,[61] in unadjusted analyses, Medicaid beneficiaries had lower rates of coronary revascularization and higher rates of in-hospital mortality compared with privately insured individuals. Similar results were found in a propensity-matched cohorts. Further studies are needed to identify and understand the causes of the variation in STEMI outcomes by insurance status.

Black vs. White patients

In a US cohort of 6402 patients, self-identified black and white patients differed in several clinical and socioeconomic characteristics.[62] The higher the prevalence of characteristics associated with being black, the higher the 5-year mortality rate, but no differences were observed between black and white patients with similar characteristics. Thus, a greater prevalence of characteristics associated with black race, but not race itself, was associated with higher mortality risk after AMI.

Conclusions

Important data from large randomized trials have augmented the management of patients presenting with ACS. Importantly, recognition of the clinical spectrum of ACS has expanded in recent years and atypical forms, besides the classical STEMI and NSTEMI, such as takotsubo syndrome, coronary dissection, MINOCA, and myocarditis (**Figure 6**) have been increasingly recognized, characterized and their causes and mechanisms defined. The management of these novel forms of ACS is still not evidence-based, but significant progress has been made recently. Furthermore, disparities in the implementation of guideline-based therapies are increasingly addressed to the benefit of the patient population at large.

ljeno na dokazima, no nedavno su postignuti znatni napredci. Nadalje, razlike u implementaciji terapija temeljenih na dokazima pojačano se naglašavaju u korist široke populacije bolesnika.

FIGURE 6. *Take home figure* The spectrum of acute coronary syndromes encompasses plaque rupture and erosion (=Type 1 myocardial infarction), Type 2 myocardial infarction, epicardial and microvascular coronary spasm, coronary embolism, acute myocarditis, takotsubo syndrome, and coronary dissection.

LITERATURE ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||

1. Lüscher TF, Obeid S. From Eisenhower's heart attack to modern management: a true success story! Eur Heart J. 2017;38:3066-9. https://doi.org/10.1093/eurheartj/ehx569

2. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, et al. Improved outcomes in patients with ST-elevation myocardial infarction during the last 20 years are related to implementation of evidence-based treatments: experiences from the SWEDEHEART registry 1995-2014. Eur Heart J. 2017;38:3056-65. https://doi.org/10.1093/eurheartj/ehx515

3. Adlam D, Alfonso F, Maas A, Vrints C. Writing Committee. European Society of Cardiology, acute cardiovascular care association, SCAD study group: a position paper on spontaneous coronary artery dissection. Eur Heart J. 2018;39:3353-68. https://doi.org/10.1093/eurheartj/ehy080

4. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International Expert Consensus Document on Takotsubo Syndrome (Part I): clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J. 2018;39:2032-46. https://doi.org/10.1093/eurheartj/ehy076

5. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, et al. International Expert Consensus Document on Takotsubo Syndrome (Part II): diagnostic workup, outcome, and management. Eur Heart J. 2018;39:2047-62. https://doi.org/10.1093/eurheartj/ehy077

6. Niccoli G, Scalone G, Crea F. Acute myocardial infarction with no obstructive coronary atherosclerosis: mechanisms and management. Eur Heart J. 2015;36:475-81. https://doi.org/10.1093/eurheartj/ehu469

7. Ekström K, Lehtonen J, Nordenswan HK, Mayranpaa MI, Raisanen-Sokolowski A, Kandolin R, et al. Sudden death in cardiac sarcoidosis: an analysis of nationwide clinical and cause-of-death registries. Eur Heart J. 2019;40:3121-8. https://doi.org/10.1093/eurheartj/ehz428

8. Khera AV, Chaffin M, Zekavat SM, Collins RL, Roselli C, Natarajan P, et al. Whole-genome sequencing to characterize monogenic and polygenic contributions in patients hospitalized with early-onset myocardial infarction. Circulation. 2019;139:1593-602. https://doi.org/10.1161/CIRCULATIONAHA.118.035658

9. Libby P, Pasterkamp G, Crea F, Jang IK. Reassessing the mechanisms of acute coronary syndromes. Circ Res. 2019;124:150-60. https://doi.org/10.1161/CIRCRESAHA.118.311098

10. Tan Y, Sheng Z, Zhou P, Liu C, Zhao H, Song L, et al. Plasma trimethylamine N-oxide as a novel biomarker for plaque rupture in patients with ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv. 2019;12:e007281. https://doi.org/10.1161/CIRCINTERVENTIONS.118.007281

11. Vergallo R, Porto I, D'Amario D, Annibali G, Galli M, Benenati S, et al. Coronary atherosclerotic phenotype and plaque healing in patients with recurrent acute coronary syndromes compared with patients with long-term clinical stability: an in vivo optical coherence tomography study. JAMA Cardiol. 2019;4:321-9. https://doi.org/10.1001/jamacardio.2019.0275

12. Fracassi F, Crea F, Sugiyama T, Yamamoto E, Uemura S, Vergallo R, et al. Healed culprit plaques in patients with acute coronary syndromes. J Am Coll Cardiol. 2019;73:2253-63. https://doi.org/10.1016/j.jacc.2018.10.093

13. Herring N, Tapoulal N, Kalla M, Ye X, Borysova L, Lee R, et al. Oxford Acute Myocardial Infarction (OxAMI) Study. Neuropeptide-Y causes coronary microvascular constriction and is associated with reduced ejection fraction following ST-elevation myocardial infarction. Eur Heart J. 2019;40:1920-9. https://doi.org/10.1093/eurheartj/ehz115

14. Altwegg LA, Neidhart M, Hersberger M, Muller S, Eberli FR, Corti R, et al. Myeloid-related protein 8/14 complex is released by monocytes and granulocytes at the site of coronary occlusion: a novel, early, and sensitive marker of acute coronary syndromes. Eur Heart J. 2007;28:941-8. https://doi.org/10.1093/eurheartj/ehm078

15. Marinković G, Grauen Larsen H, Yndigegn T, Szabo IA, Mares RG, de Camp L, et al. Inhibition of pro-inflammatory myeloid cell responses by short-term S100A9 blockade improves cardiac function after myocardial infarction. Eur Heart J. 2019;40:2713-23. https://doi.org/10.1093/eurheartj/ehz461

16. Tang TWH, Chen HC, Chen CY, Yen CYT, Lin CJ, Prajnamitra RP, et al. Loss of gut microbiota alters immune system composition and cripples postinfarction cardiac repair. Circulation. 2019;139:647-59. https://doi.org/10.1161/CIRCULATIONAHA.118.035235

17. Scally C, Abbas H, Ahearn T, Srinivasan J, Mezincescu A, Rudd A, et al. Myocardial and systemic inflammation in acute stress-induced (takotsubo) cardiomyopathy. Circulation. 2019;139:1581-92. https://doi.org/10.1161/CIRCULATIONAHA.118.037975

18. Templin C, Hanggi J, Klein C, Topka MS, Hiestand T, Levinson RA, et al. Altered limbic and autonomic processing supports brain-heart axis in takotsubo syndrome. Eur Heart J. 2019;40:1183-7. https://doi.org/10.1093/eurheartj/ehz068

19. Boeddinghaus J, Nestelberger T, Twerenbold R, Neumann JT, Lindahl B, Giannitsis E, et al.; APACE, BACC, and TRAPID-AMI Investigators. Impact of age on the performance of the ESC 0/1h-algorithms for early diagnosis of myocardial infarction. Eur Heart J. 2018;39:3780-94. https://doi.org/10.1093/eurheartj/ehy514

20. Twerenbold R, Costabel JP, Nestelberger T, Campos R, Wussler D, Arbucci R, et al. Outcome of applying the ESC 0/1-hour algorithm in patients with suspected myocardial infarction. J Am Coll Cardiol. 2019;74:483-94. https://doi.org/10.1016/j.jacc.2019.05.046

21. Januzzi JLJr. Mahler SA, Christenson RH, Rymer J, Newby LK, Body R, Morrow DA, Jaffe AS. Recommendations for institutions transitioning to high-sensitivity troponin testing: JACC Scientific Expert Panel. J Am Coll Cardiol. 2019;73:1059-77.

22. Gibson CM, Holmes D, Mikdadi G, Presser D, Wohns D, Yee MK, et al. Eberly AL3rd, Iteld B, Krucoff MW. Implantable cardiac alert system for early recognition of ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2019;73:1919-27. https://doi.org/10.1016/j.jacc.2019.01.014

23. Mani P, Puri R, Schwartz GG, Nissen SE, Shao M, Kastelein JJP, et al. Association of initial and serial C-reactive protein levels with adverse cardiovascular events and death after acute coronary syndrome: a secondary analysis of the VISTA-16 trial. JAMA Cardiol. 2019;4:314-20. https://doi.org/10.1001/jamacardio.2019.0179

24. sleh R, Enriquez-Sarano M, Jaffe AS, Manemann SM, Weston SA, Jiang R, et al. Galectin-3 levels and outcomes after myocardial infarction: a population-based study. J Am Coll Cardiol. 2019;73:2286-95. https://doi.org/10.1016/j.jacc.2019.02.046

25. Farag M, Spinthakis N, Gue YX, Srinivasan M, Sullivan K, Wellsted D, et al. Impaired endogenous fibrinolysis in ST-segment elevation myocardial infarction patients undergoing primary percutaneous coronary intervention is a predictor of recurrent cardiovascular events: the RISK PPCI study. Eur Heart J. 2019;40:295-305. https://doi.org/10.1093/eurheartj/ehy656

26. Li XS, Obeid S, Wang Z, Hazen BJ, Li L, Wu Y, et al. Trimethyllysine, a trimethylamine N-oxide precursor, provides near- and long-term prognostic value in patients presenting with acute coronary syndromes. Eur Heart J. 2019;40:2700-9. https://doi.org/10.1093/eurheartj/ehz259

27. Guerin M, Silvain J, Gall J, Darabi M, Berthet M, Frisdal E, et al. Association of serum cholesterol efflux capacity with mortality in patients with ST-segment elevation myocardial infarction. J Am Coll Cardiol. 2018;72:3259-69. https://doi.org/10.1016/j.jacc.2018.09.080

28. Lindholm D, James SK, Gabrysch K, Storey RF, Himmelmann A, Cannon CP, et al. Association of multiple biomarkers with risk of all-cause and cause-specific mortality after acute coronary syndromes: a secondary analysis of the PLATO biomarker study. JAMA Cardiol. 2018;3:1160-6. https://doi.org/10.1001/jamacardio.2018.3811

29. Androulakis AFA, Zeppenfeld K, Paiman EHM, Piers SRD, Wijnmaalen AP, Siebelink HJ, et al. Entropy as a novel measure of myocardial tissue heterogeneity for prediction of ventricular arrhythmias and mortality in post-infarct patients. JACC Clin Electrophysiol. 2019;5:480-9. https://doi.org/10.1016/j.jacep.2018.12.005

30. Schupke S, Neumann FJ, Menichelli M, Mayer K, Bernlochner I, Wohrle J, et al. ISAR-REACT 5 Trial Investigators. Ticagrelor or prasugrel in patients with acute coronary syndromes. N Engl J Med. 2019;381:1524-34. https://doi.org/10.1056/NEJMoa1908973

31. Redfors B, Dworeck C, Haraldsson I, Angeras O, Odenstedt J, Ioanes D, et al. Pretreatment with P2Y12 receptor antagonists in ST-elevation myocardial infarction: a report from the Swedish Coronary Angiography and Angioplasty Registry. Eur Heart J. 2019;40:1202-10.

32. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39:119-77.

33. Abtan J, Steg PG. Pre-treatment with a P2Y12 antagonist before PCI in STEMI: why should we wait? Eur Heart J. 2019;40:1211-3. https://doi.org/10.1093/eurheartj/ehz058

34. Lemkes JS, Janssens GN, van der Hoeven NW, van de Ven PM, Marques KMJ, Nap A, et al. Timing of revascularization in patients with transient ST-segment elevation myocardial infarction: a randomized clinical trial. Eur Heart J. 2019;40:283-91. https://doi.org/10.1093/eurheartj/ehy651

35. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, et al.; COMPLETE Trial Steering Committee and Investigators. Complete revascularization with multivessel PCI for myocardial infarction. N Engl J Med. 2019;381:1411-21. https://doi.org/10.1056/NEJMoa1907775

36. Stone GW, Genereux P, Harrington RA, White HD, Gibson CM, Steg PG, et al. Impact of lesion complexity on peri-procedural adverse events and the benefit of potent intravenous platelet adenosine diphosphate receptor inhibition after percutaneous coronary intervention: core laboratory analysis from 10 854 patients from the CHAMPION PHOENIX trial. Eur Heart J. 2018;39:4112-21. https://doi.org/10.1093/eurheartj/ehy562

37. Fujino A, Kadohira T, Redfors B, Maehara A, Serruys PW, Mintz GS, et al. Significant association among residual SYNTAX score, non-culprit major adverse cardiac events, and greyscale and virtual histology intravascular ultrasound findings: a substudy from the PROSPECT study. EuroIntervention. 2019;14:1676-84. https://doi.org/10.4244/EIJ-D-18-00681

38. Johnson TW, Raber L, di Mario C, Bourantas C, Jia H, Mattesini A, et al. Clinical use of intracoronary imaging. Part 2: acute coronary syndromes, ambiguous coronary angiography findings, and guiding interventional decision-making: an expert consensus document of the European Association of Percutaneous Cardiovascular Interventions. Eur Heart J. 2019;40:2566-84. https://doi.org/10.1093/eurheartj/ehz332

39. Aradi D, Gross L, Trenk D, Geisler T, Merkely B, Kiss RG, et al. Platelet reactivity and clinical outcomes in acute coronary syndrome patients treated with prasugrel and clopidogrel: a pre-specified exploratory analysis from the TROPICAL-ACS trial. Eur Heart J. 2019;40:1942-51. https://doi.org/10.1093/eurheartj/ehz202

40. De Maria GL, Alkhalil M, Wolfrum M, Fahrni G, Borlotti A, Gaughran L, et al. Index of microcirculatory resistance as a tool to characterize microvascular obstruction and to predict infarct size regression in patients with STEMI undergoing primary PCI. JACC Cardiovasc Imaging. 2019;12:837-48. https://doi.org/10.1016/j.jcmg.2018.02.018

41. Nepper-Christensen L, Lønborg J, Høfsten DE, Ahtarovski KA, Kyhl K, Göransson C, et al. Impact of diagnostic ECG-to-wire delay in STEMI patients treated with primary PCI: a DANAMI-3 substudy. EuroIntervention. 2018;14:700-7. https://doi.org/10.4244/EIJ-D-17-00857

42. De Maria GL, Cuculi F, Patel N, Dawkins S, Fahrni G, Kassimis G, et al. How does coronary stent implantation impact on the status of the microcirculation during primary percutaneous coronary intervention in patients with ST-elevation myocardial infarction? Eur Heart J. 2015;36:3165-77. https://doi.org/10.1093/eurheartj/ehv353

43. Morales-Ponce FJ, Lozano-Cid FJ, Martinez-Romero P, Gonzalez-Perez P, Sanchez-Brotons JA, Diaz-Torres I, et al. Intracoronary tenecteplase versus abciximab as adjunctive treatment during primary percutaneous coronary intervention in patients with anterior myocardial infarction. EuroIntervention. 2019;14:1668-75. https://doi.org/10.4244/EIJ-D-18-00885

44. McCartney PJ, Eteiba H, Maznyczka AM, McEntegart M, Greenwood JP, Muir DF, et al. T-TIME Group. Effect of low-dose intracoronary alteplase during primary percutaneous coronary intervention on microvascular obstruction in patients with acute myocardial infarction: a randomized clinical trial. JAMA. 2019;321:56-68.

45. Mathias WJr. Tsutsui JM, Tavares BG, Fava AM, Aguiar MOD, Borges BC, et al; MRUSMI Investigators. Sonothrombolysis in ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention. J Am Coll Cardiol. 2019;73:2832-42.

46. Hausenloy DJ, Kharbanda RK, Moller UK, Ramlall M, Aaroe J, Butler R, et al. CONDI-2/ERIC-PPCI Investigators. Effect of remote ischaemic conditioning on clinical outcomes in patients with acute myocardial infarction (CONDI-2/ERIC-PPCI): a single-blind randomised controlled trial. Lancet. 2019;394:1415-24. https://doi.org/10.1016/S0140-6736(19)32039-2

47. Hall M, Bebb OJ, Dondo TB, Yan AT, Goodman SG, Bueno H, et al. Guideline-indicated treatments and diagnostics, GRACE risk score, and survival for non-ST elevation myocardial infarction. Eur Heart J. 2018;39:3798-806. https://doi.org/10.1093/eurheartj/ehy517

48. Szummer K, Wallentin L, Lindhagen L, Alfredsson J, Erlinge D, Held C, et al. Relations between implementation of new treatments and improved outcomes in patients with non-ST-elevation myocardial infarction during the last 20 years: experiences from SWEDEHEART registry 1995 to 2014. Eur Heart J. 2018;39:3766-76. https://doi.org/10.1093/eurheartj/ehy554

49. Doimo S, Fabris E, Piepoli M, Barbati G, Antonini-Canterin F, Bernardi G, et al. Impact of ambulatory cardiac rehabilitation on cardiovascular outcomes: a long-term follow-up study. Eur Heart J. 2019;40:678-85. https://doi.org/10.1093/eurheartj/ehy417

50. Jones DA, Rathod KS, Koganti S, Lim P, Firoozi S, Bogle R, et al. The association between the public reporting of individual operator outcomes with patient profiles, procedural management, and mortality after percutaneous coronary intervention: an observational study from the Pan-London PCI (BCIS) Registry using an interrupted time series analysis. Eur Heart J. 2019;40:2620-9. https://doi.org/10.1093/eurheartj/ehz152

51. Berg DD, Wiviott SD, Braunwald E, Guo J, Im K, Kashani A, et al. Modes and timing of death in 66 252 patients with non-ST-segment elevation acute coronary syndromes enrolled in 14 TIMI trials. Eur Heart J. 2018;39:3810-20. https://doi.org/10.1093/eurheartj/ehy556

52. Bradley SM, Borgerding JA, Wood GB, Maynard C, Fihn SD. Incidence, risk factors, and outcomes associated with in-hospital acute myocardial infarction. JAMA Netw Open. 2019;2:e187348. https://doi.org/10.1001/jamanetworkopen.2018.7348

53. Saw J, Starovoytov A, Humphries K, Sheth T, So D, Minhas K, et al. Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. Eur Heart J. 2019;40:1188-97. https://doi.org/10.1093/eurheartj/ehz007

54. Gili S, Cammann VL, Schlossbauer SA, Kato K, D'Ascenzo F, Di Vece D, et al. Cardiac arrest in takotsubo syndrome: results from the InterTAK Registry. Eur Heart J. 2019;40:2142-51. https://doi.org/10.1093/eurheartj/ehz170

55. Cammann VL, Sarcon A, Ding KJ, Seifert B, Kato K, Di Vece D, et al. Clinical features and outcomes of patients with malignancy and takotsubo syndrome: observations from the International Takotsubo Registry. J Am Heart Assoc. 2019;8:e010881. https://doi.org/10.1161/JAHA.118.010881

56. Dreyer RP, Tavella R, Curtis JP, Wang Y, Pauspathy S, Messenger J, et al. Myocardial infarction with non-obstructive coronary arteries as compared with myocardial infarction and obstructive coronary disease: outcomes in a Medicare population. Eur Heart J. 2020 Feb 14;41(7):870-878. https://doi.org/10.1093/eurheartj/ehz403

57. Stehli J, Martin C, Brennan A, Dinh DT, Lefkovits J, Zaman S. Sex differences persist in time to presentation, revascularization, and mortality in myocardial infarction treated with percutaneous coronary intervention. J Am Heart Assoc. 2019;8:e012161. https://doi.org/10.1161/JAHA.119.012161

58. Meyer MR, Bernheim AM, Kurz DJ, O'Sullivan CJ, Tüller D, Zbinden R, et al. Gender differences in patient and system delay for primary percutaneous coronary intervention: current trends in a Swiss ST-segment elevation myocardial infarction population. Eur Heart J Acute Cardiovasc Care. 2019;8:283-90. https://doi.org/10.1177/2048872618810410

59. Hao Y, Liu J, Liu J, Yang N. Smith SCJr, Huo Y, et al. Sex differences in in-hospital management and outcomes of patients with acute coronary syndrome. Circulation. 2019;139:1776–85. https://doi.org/10.1161/CIRCULATIONAHA.118.037655

60. Vicent L, Ariza-Solé A, Alegre O, Sanchís J, López-Palop R, Formiga F, et al. Octogenarian women with acute coronary syndrome present frailty and readmissions more frequently than men. Eur Heart J Acute Cardiovasc Care. 2019;8:252–63. https://doi.org/10.1177/2048872618798226

61. Patel N, Gupta A, Doshi R, Kalra R, Bajaj NS, Arora G, et al. In-hospital management and outcomes after ST-segment-elevation myocardial infarction in Medicaid beneficiaries compared with privately insured individuals. Circ Cardiovasc Qual Outcomes. 2019;12:e004971. https://doi.org/10.1161/CIRCOUTCOMES.118.004971

62. Graham GN, Jones PG, Chan PS, Arnold SV, Krumholz HM, Spertus JA. Racial disparities in patient characteristics and survival after acute myocardial infarction. JAMA Netw Open. 2018;1:e184240. https://doi.org/10.1001/jamanetworkopen.2018.4240