Godina 2021. u kardiovaskularnoj medicini: intervencijska kardiologija

The year in cardiovascular medicine 2021: interventional cardiology

Javier Escaned[1]*, Farouc A. Jaffer[2], Julinda Mehilli[3], Roxana Mehran[4]

[1]Hospital Clínico San Carlos IDISCC, Complutense University of Madrid, Madrid, Spain

[2]Cardiology Division, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

[3]Medizinische Klinik I, Landshut-Achdorf Hospital, Landshut, Klinikum der Universitaet München, Ludwig-Maximilians-Universitaet and German Centre for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Munich, Germany

[4]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

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SAŽETAK: Od objavljivanja prošlogodišnjeg izvješća u časopisu *European Heart Journal* ostvaren je znatan napredak u svim granama intervencijske kardiologije. Do tog je napretka došlo usprkos kontinuiranomu globalnom opterećenju zdravstvenih djelatnika i zdravstvenih sustava pandemijom bolesti COVID-19. Ovogodišnje izvješće pruža uvid u novosti o perkutanim koronarnim intervencijama, o intervencijama pri strukturnim bolestima srca i o popratnoj farmakoterapiji.

SUMMARY: Since last year's report in the European Heart Journal, we have witnessed substantial progress in all aspects of interventional cardiology. Of note, the practice of interventional cardiology took place amidst successive waves of the COVID-19 pandemic, which continues to be a major burden for all healthcare professionals around the globe. In our yearly review, we shall revisit the developments in percutaneous coronary intervention, structural heart interventions, and adjunctive pharmacotherapy.

KLJUČNE RIJEČI: intervencijska kardiologija, koronarne intervencije, transkateterska zamjena aortalnog zalistka, antiagregacijski lijekovi.

KEYWORDS: interventional cardiology, coronary interventions, transcatheter aortic valve implantation, antiplatelet agents.

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***ADDRESS FOR CORRESPONDENCE**: Javier Escaned, Hospital Clínico San Carlos IDISCC, Complutense University of Madrid, Madrid, Spain. / Phone: +34 91 3303438, Fax: +34 91 3303289 / E-mail: escaned@secardiologia.es

ORCID: Javier Escaned, https://orcid.org/0000-0003-4932-0112 • Farouc A. Jaffer, https://orcid.org/0000-0001-7980-384X Julinda Mehilli, https://orcid.org/0000-0002-8750-5567 • Roxana Mehran, https://orcid.org/0000-0002-5546-262X

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Uvod

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Introduction

Since last year's report in the European Heart Journal, we have witnessed substantial progress

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in all aspects of interventional cardiology. Of note, the practice of interventional cardiology took place amidst successive waves of the COVID-19 pandemic, which continues to be a major burden for all healthcare professionals around the globe. In our yearly review, we shall revisit the developments in percutaneous coronary intervention (PCI), structural heart interventions, and adjunctive pharmacotherapy, (**Figure 1A**).

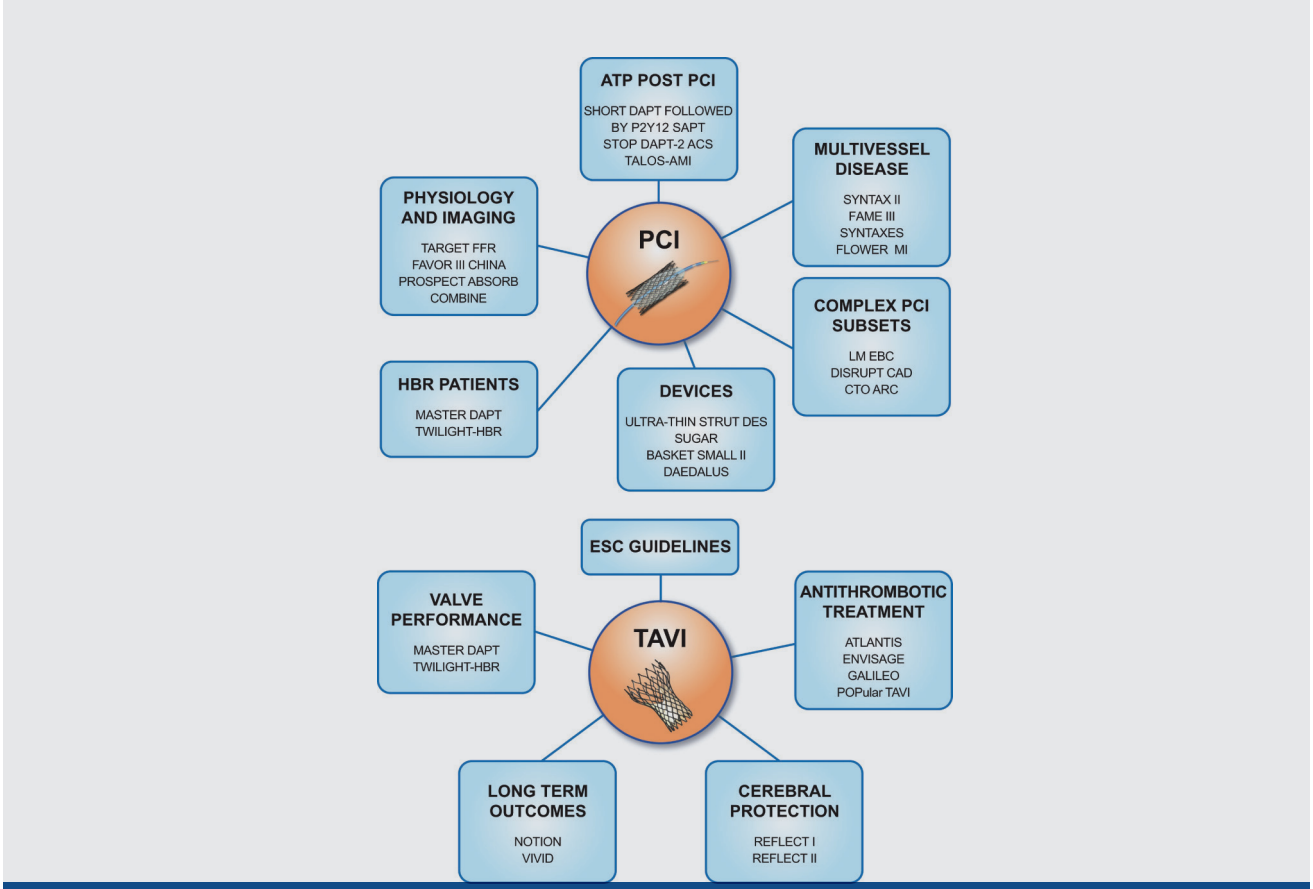

FIGURE 1A GRAPHICAL ABSTRACT. Graphical abstract summarizing relevant studies published over the last year in the field of percutaneous coronary interventions and transcatheter aortic valve implantation. (from Escaned J, Jaffer FA, Mehilli J, Mehran R. The year in cardiovascular medicine 2021: interventional cardiology. Eur Heart J. 2022 Feb 3;43(5):377-386. doi: 10.1093/eurheartj/ehab884, by permission of OUP on behalf of the ESC).

Revaskularizacija *non-culprit* lezija u akutnom infarktu miokarda s elevacijom ST-segmenta

Uloga potpune revaskularizacije miokarda u bolesnika s akutnim koronarnim sindromom (AKS) i višežilnom koronarnom bolesti srca (VKB) i dalje je u fokusu velikoga broja istraživača i kliničara, a napose nakon objavljivanja rezultata istraživanja *COMPLETE*. Naime, podanalize istraživanja *COMPLETE* i *COMPARE-ACUTE* upozorile su na povoljan učinak potpune revaskularizacije u akutnom infarktu miokarda s elevacijom ST-segmenta (STEMI). Potpuna revaskularizacija u spomenutim je istraživanjima obuhvaćala i *non-culprit* lezije (NCL) s angiografski procijenjenim suženjem lumena ≥70 %, odnosno s funkcijski znatnim suženjem procijenjenim vrijednosti-

Non-culprit lesion revascularization in ST-segment elevation myocardial infarction

In the aftermath of the COMPLETE trial, the completeness of revascularization in patients with acute coronary syndrome (ACS) and multivessel disease (MVD) continues to attract the attention of investigators and clinicians. Subanalyses from the COMPLETE and COMPARE-ACUTE trials suggest that, in the context of ST-segment elevation myocardial infarction (STEMI), complete revascularization provides a benefit when treating non-culprit lesions (NCLs) fulfilling either visually estimated angiographic stenosis of ≥70% or intracoronary fractional flow reserve (FFR)≤0.80 severity criteria.[1,2] From these two trials,

ma ≤0,80 s pomoću intrakoronarnog FFR-a (*fractional flow reserve*).[1,2] Na temelju zaključaka spomenutih istraživanja, kao i onog studije *FAME* s FFR-om (koje je prethodno potvrdilo učinkovitost FFR-a u VKB-u), očekivalo se da će primjena funkcijske procjene u PCI NCL-a u STEMI-ju rezultirati poboljšanjem kliničkih ishoda. Međutim, ovo se nije pokazalo točnim u nedavno objavljenom istraživanju *FLOWER-MI*[3]. U sklopu navedenoga, 1163 bolesnika sa STEMI-jem i VKB-om nasumično su liječena revaskularizacijom NCL-a, bilo na temelju angiografskih bilo na osnovi funkcijskih kriterija. U usporedbi s revaskularizacijom NCL-a prema angiografskoj značajnosti, revaskularizacija prema funkcijskoj značajnosti lezije nije pružila prednost ni u preživljenju bolesnika ni u incidenciji novog infarkta miokarda, a ni u potrebi za hitnom revaskularizacijom tijekom praćenja od godine dana. Naknadno se, podanalizom istraživanja *FLOWER-MI*, pokazalo kako su bolesnici u kojih je provedena potpuna revaskularizacija NCL-a vođena funkcijskom procjenom imali manju učestalost nepoželjnih događaja od bolesnika u kojih je sama revaskularizacija NCL-a odgođena.[4] Ovo je sukladno rezultatima nedavno objavljene velike metaanalize[5], koja je obuhvatila 8579 bolesnika. U toj je metaanalizi učestalost nepoželjnih događaja bila veća među bolesnicima s AKS-om u kojih je odgođena revaskularizacija NCL-a (prema FFR-u), nego među bolesnicima sa stabilnom koronarnom bolesti srca. Ovo je moguće posljedično, s jedne strane, smanjenoj točnosti FFR-a u procjeni značajnosti NCL-a u bolesnika sa STEMI-jem ili protektivnom učinku PCI-ja u NCL-u s vulnerabilnim plakovima sklonima rupturi. Stoga, ako je tehnički izvediva, PCI znatno suženih NCL-a u žila većih od 2 mm u promjeru indicirana je u svih bolesnika sa STEMI-jem, a neovisno o vrijednostima FFR-a.[6]

Revaskularizacija u višežilnoj koronarnoj bolesti srca

Petogodišnji ishodi istraživanja *SYNTAX II* pokazali su prednosti sjedinjenja najboljih praksi u PCI-ju (poput intervencija vođenih slikovnim metodama i funkcijskom procjenom, uporabe stentova s tankim strukturnim nitima *strutovima*, te kompletne revaskularizacije) u jedinstvenu revaskularizacijsku strategiju liječenja bolesnika s trožilnom koronarnom bolešću srca (3KB) nazvanu „SYNTAX II strategijom".[7] Nakon razdoblja od pet godina učestalost nepovoljnih kardiovaskularnih događaja (MACCE) među bolesnicima iz istraživanja *SYNTAX II* bila je mnogo niža nego među sličnim bolesnicima iz istraživanja *SYNTAX-I PCI* (21,5 % prema 36,4 %, P <0,001; **slika 1B**). Niža je bila učestalost ponovne revaskularizacije (13,8 % prema 23,8 %, P <0,001) i novog infarkta miokarda (2,7 % prema 10,4 %, P <0,001), a to se pak odnosilo i na periproceduralni infarkt (0,2 % prema 3,8 %, P <0,001) i na spontani infarkt miokarda (2,3 % prema 6,9 %, P = 0,004). Među ispitanicima iz istraživanja *SYNTAX II* niža je bila i sveukupna smrtnost (8,1 % prema 13,8 %, P = 0,013), pretežito kao odraz nižih stopa kardiovaskularne smrtnosti (2,8 % prema 8,4 %, P <0,001). Učeand based on the classic FFR FAME trial results, one might expect that gauging the need for PCI in NCLs of STEMI with FFR should result in better clinical outcomes. However, the recently published FLOWER-MI trial,[3] which randomly assigned 1163 patients with STEMI and MVD to perform PCI in NCLs guided by either FFR or angiography, found that the FFR-guided strategy did not provide a significant benefit over an angiography-guided strategy with respect to the risk of death, MI, or urgent revascularization at 1 year. Subsequently, a substudy of the FLOWER-MI found that patients in the FFR guidance arm with ≥1 PCI had lower event rates at 1 year, compared with patients with a deferred PCI.[4] These findings align with a recent large patient-level metanalysis[5] (n=8579) that found increased event rates associated with an FFR-based deferral of revascularization of NCLs in ACS, compared with stable patients, pointing to either suboptimal performance of non-culprit FFR in STEMI patients or a protective effect of PCI in NCLs with rupture-prone vulnerable plaques. Overall, PCI of severely stenotic NCLs in ≥2.0 mm diameter arteries is indicated for STEMI patients, regardless of the FFR status, when technically feasible.[6]

Revascularization in multivessel coronary disease

The 5-year outcomes of the SYNTAX II trial showcase the benefits of integrating best practices of PCI (imaging- and physiological-PCI guidance, thin-strut stents, and more complete revascularization) into a single revascularization strategy (SYNTAX II strategy) in treating patients with three-vessel coronary disease (3VD).[7] At 5 years, major adverse cardiac and cerebral events (MACCEs) in SYNTAX II were significantly lower than in a matched cohort of SYNTAX-I PCI patients (21.5 vs. 36.4%, P, 0.001; (**Figure 1B**), with lower rates of revascularization (13.8 vs. 23.8%, P,0.001), and MI (2.7 vs. 10.4%, P,0.001), consisting of both procedural MI (0.2 vs. 3.8%, P,0.001) and spontaneous MI (2.3 vs. 6.9%, P=0.004). All-cause mortality was lower in SYNTAX II (8.1 vs. 13.8%, P=0.013) reflecting a lower rate of cardiac death (2.8 vs. 8.4%, P,0.001). Major adverse cardiac and cerebral event outcomes at 5 years among patients in SYNTAX II and pre-defined patients in the SYNTAX-I coronary artery bypass graft (CABG) cohort were similar (21.5 vs. 24.6%, P=0.35).

The results of the FAME III randomized clinical trial (RCT), which compared from a non-inferiority standpoint of the clinical outcomes of 1500 patients with 3VD randomized to either the FFR-guided PCI or CABG, were published.[8] At 1-year follow-up, MACCE rate in FAME III was 10.6 and 6.9% among patients assigned to PCI and CABG, respectively [hazard ratio (HR)=1.5, 95% confidence interval (CI 1.1–2.2)]; thus, non-inferiority of the FFR-guided PCI was not reached (P=0.35 for non-inferiority; (**Figure 1B**). Notwithstanding the differences in the study design, at first glance, the results of FAME III seem

FIGURE 1B. Please see Figure 1 in the original article.

stalost nepovoljnih kardiovaskularnih i cerebrovaskularnih događaja nakon pet godina praćenja bila je slična među ispitanicima iz istraživanja *SYNTAX II* i *SYNTAX-I CABG* (21,5 % prema 24,6 %, P = 0,35).

Nedavno su objavljeni rezultati randomiziranoga kliničkog istraživanja *FAME III* koje je među populacijom od 1500 bolesnika s 3KB-om ispitivalo neinferiornost FFR-om vođene PCI u usporedbi s CABG-om.[8] Nakon jednogodišnjega praćenja učestalost MACCE-a bila je 10,6 % među bolesnicima liječenim PCI-jem, odnosno 6,9% među bolesnicima liječenima CABG-om (omjer ugroženosti = 1,5, 95 % interval pouzdanosti: 1,1 – 2,2). Stoga istraživanje *FAME III* nije pokazalo neinferiornost FFR-om vođene PCI u odnosu prema CABG-u (P = 0,035 za neinferiornost, **slika 1B**). Ne uzimajući u obzir razlike u dizajnu istraživanja, rezultati studije *FAME III* na prvi su pogled proturječni rezultatima istraživanja *SYNTAX II*. Međutim, važno je istaknuti kako je u istraživanju *FAME III* proučavana važnost FFR-om vođene revaskularizacije, dok je u sklopu istraživanja *SYNTAX II* (i „strategije") primijenjen niz (slikovnih i funkcijskih) dijagnostičkih testova u donošenju odluke o revaskularizaciji. Dakle, za razliku od istraživanja *SYNTAX II*, u *FAME III* uključivani su bolesnici u kojih je CABG, kao optimalni modalitet liječenja, dodijeljen prema *SYNTAX II* skoru, tek uz sporadičnu uporabu dodatnih koronarnih slikovnih metoda (12 % prema 87 % u istraživanju SYNTAX II). Stoga bi buduća randomizirana istraživanja koja će uspoređivati PCI i CABG u bolesnika s VKB-om trebala uzimati u obzir najbolju postojeću ujedinjenu praksu revaskularizacije miokarda (a koja će uključivati stratifikaciju bolesnika prema *Heart Teamu*, primjenu dodatnih koronarnih slikovnih i funkcijskih metoda, procjenu mogućnosti PCI-ja u kompleksnim anatomskim odnosima, te optimalnu medikamentnu terapiju koronarne bolesti srca).

Na temelju rezultata istraživanja *SYNTAX Extended Survival* (*SYNTAXES*) razvijen je novi indeks pod nazivom *SYNTAX score II 2020* (*SS II 2020*). Svrha je tog indeksa predviđanje desetogodišnjih ishoda bolesnika s VKB-om nakon perkutane, odnosno nakon kirurške revaskularizacije. U spomenutih se bolesnika SS II 2020 pokazao učinkovitim u diferenciranju desetogodišnje smrtnosti (C-indeks za PCI = 0,73, 95 % interval pouzdanosti 0,69 – 0,76; C-indeks za CABG = 0,73, 95 % interval pouzdanosti 0,69 – 0,76) i petogodišnje pojavnosti MACCE-a (C-indeks za PCI = 0,65, 95 % interval pouzdanosti 0,61 – 0,69; C-indeks za CABG = 0,71, 95 % interval pouzdanosti 0,67 – 0,75). Potencijalna važnost spomenutog indeksa jest u tome što pomaže kliničarima, bolesnicima i njihovim obiteljima u odabiru optimalnog modaliteta revaskularizacije miokarda.[9] Iz istraživanja *SYNTAXES* dodatno se izdvaja činjenica kako ženski spol nije bio neovisni pretskazatelj desetogodišnje smrtnosti od višežilne koronarne bolesti.[10] Samo istraživanje također ističe važnost primjene optimalne medikamentne terapije nakon provedene koronarne revaskularizacije.[11]

Novi stentovi obloženi lijekom i novi baloni obloženi lijekom

Utjecaj tehnoloških poboljšanja kod stentova obloženih lijekom bio je u središtu pozornosti nekoliko radova. Utjecaj smanjenja debljine niti stentova na poboljšanje ishoda perkutanih koronarnih intervencija bio je predmet istraživanja metaanalize od 16 randomiziranih kliničkih istraživanja (20 701 bolesnik) koje su uspoređivale DES-ove s ultratankim *strutovima* i standardne DES-ove druge generacije s tankim

discordant with those of SYNTAX II. However, it is noteworthy that FAME III explored the specific value of the FFR-based revascularization, and not that of an array of clinical practices (including imaging- and physiological-guidance) encompassed into the SYNTAX II strategy. Thus, at a difference with SYNTAX II, FAME III enrolled patients with CABG recommended as the preferred treatment according to the SYNTAX score II, and intracoronary imaging was seldom used (12 vs. 87% in SYNTAX II). Future randomized studies of CABG vs. PCI might focus on whether integrated best practices (i.e. heart team-based patient stratification, use of intracoronary physiology and imaging, PCI competence in anatomical complex subsets, and optimal medical treatment) in patients with MVD.

Based on the SYNTAX Extended Survival study (SYNTAXES), a new index, named SYNTAX score II 2020 (SS II 2020), was derived to perform the prediction of 10-year outcomes after PCI or CABG in patients with MVD. The SS II 2020 demonstrated a discriminative ability in the PCI and CABG groups for predicting 10-year all- cause deaths [C-index=0.73, (95% CI 0.69–0.76) for PCI and C-index=0.73, (95% CI 0.69–0.76) for CABG] and 5-year major adverse cardiovascular events (MACEs) [C-index=0.65, (95% CI 0.61–0.69) for PCI and C-index=0.71, (95% CI 0.67–0.75) for CABG]. The index has the potential of supporting heart teams, patients, and their families in selecting the optimal revascularization modality.[9] The SYNTAXES study also reported that female sex was not an independent predictor of mortality at 10 years in patients with MVD,[10] and stressed the importance of optimal medical treatment after coronary revascularization.[11]

New drug-eluting stents and drug-coated balloons

The impact of technological improvements in drug-eluting stents (DES) has been the focus of several publications. Whether the reduction in strut thickness improves PCI outcomes was investigated in a study-level meta-analysis of 16 RCTs (20701 patients) comparing an ultrathin-strut DES to a conventional second- generation thin-strut DES.[12] At a mean follow-up of 2.5 years, the ultrathin-strut DES use reduced the risk of TLF, driven by less cardiac death-target lesion revascularization (CD-TLR) compared with the conventional second-generation thin-strut DES, with similar risks of MI, ST, cardiac death, and all-cause mortality.

The SUGAR RCT investigated the value of the Cre8 EVO stent, designed to release sirolimus with an amphiphilic carrier from laser-dug wells, in diabetic patients undergoing PCI. A total of 1175 patients were randomized to PCI with either Cre8 EVO or zotarolimus-eluting Resolute Onyx stents. At 1-year follow-up, the study revealed that Cre8 EVO stents were non-inferior to Resolute Onyx stents in terms of target lesion failure [7.2% in Cre8 EVO and 10.9% in Resolute Onyx arms, HR=0.65, (95% CI 0.44–0.96); P non-inferiority ,0.001]. An exploratory analysis for superiority at 1 year suggested the superiority of the Cre8 EVO over Resolute Onyx stents.[13]

Treatment of small coronary vessels remains a major challenge for PCI, and the use of stent-avoidance strategies has been considered in this context. A pre-specified substudy of the

strutovima.[12] Nakon prosječnog praćenja od 2,5 godine uporaba DES-ova s ultratankim *strutovima* smanjila je rizik od neuspješne revaskularizacije ciljne lezije i prati je manje srčanih smrti zbog neuspješne revaskularizacije ciljne lezije u usporedbi sa standardnim DES-ovima druge generacije s tankim *strutovima*, uz slične rizike od infarkta miokarda, tromboze stenta, kardijalne smrtnosti i ukupne smrtnosti.

Randomizirana klinička studija *SUGAR* istraživala je učinkovitost *Cre8 EVO* stenta, dizajniranog za otpuštanje sirolimusa s amfifilnim nosačem i laserski napravljenim spremnicima u dijabetičara u kojih je učinjena PCI. Nakon praćenja od godinu dana, *Cre8 EVO* bili su neinferiorni stentovima *Resolute Onyx* u smislu neuspješne revaskularizacije ciljne lezije (7,2 % u *Cre8 EVO* prema 10,9 % u *Resolute Onyx* skupini, omjer rizika = 0,65, interval pouzdanosti (0,44 – 0,96), P-neinferiornost <0,001]. Analiza o superiornosti nakon godinu dana upućuje na superiornost *Cre8 EVO* prema stentu *Resolute Onyx*.[13]

Liječenje promjena u koronarnim arterijama maloga promjera ostaje velik izazov za PCI i u takvim se situacijama razmatra uporaba metoda koje izbjegavaju postavljanje stentova. Podstudija istraživanja *BASKET-SMALL-2* analizirala je 758 bolesnika koji su nasumično raspoređeni za liječenje novonastalih lezija <3 mm s balonom obloženim lijekom (DCB) ili DES-om. Učestalost velikih neželjenih kardiovaskularnih događaja procijenjena po Kaplan-Meieru bila je 15 % u objema skupinama [omjer rizika = 0,99, (95 % interval pouzdanosti 0,68 – 1,45); P = 0,95]. Studija je pokazala kontinuiranu učinkovitost i sigurnost DCB-a u usporedbi s DES-om pri novonastalim lezijama u koronarnim arterijama maloga promjera.[14] Što se tiče liječenja restenoze stenta, nedavana metaanaliza *DEADALUS* koja je uspoređivala PCI s DCB-om u usporedbi s DES-om, pokazala je mnogo veću učestalost revaskularizacije u trogodišnjem intervalu u grupi koja je liječena DCB-om [omjer rizika = 1,58, (95 % interval pouzdanosti 1,16 –2,13)].[15]

Podskup kompleksnih koronarnih lezija

Randomizirano kliničko istraživanje *EBC-LM* uključilo je bolesnike sa suženjem debla lijeve koronarne arterije (LMCA) koje je uključivalo njezino račvište u skupini u kojoj se planirala inicijalna ugradnja jednog (n = 230) i skupinu s planiranom inicijalnom ugradnjom dvaju stentova (n = 267). Zajednički ciljni ishod od smrtnosti, infarkta miokarda i neuspješne revaskularizacije nakon 12 mjeseci nastupio je u 14,7 % bolesnika u kojih je inicijalni plan bio ugradnja jednog u usporedbi sa 17,7 % bolesnika u kojih je bila planirana implantacija dvaju stentova [omjer rizika = 0,79, (95 % interval pouzdanosti 0,5 – 1,3); P = 0,34; **slika 2**]. Vrijeme trajanja zahvata, doza zračenja i utrošak materijala podupiru primjenu pristupa s inicijalnom ugradnjom jednog stenta. Poboljšanje simptoma bilo je izvrsno i podjednako u objema skupinama. Ova saznanja podupiru inicijalnu ugradnju jednog stenta kao osnovni pristup za PCI LMCA sa zahvaćanjem njezinog račvišta, iako je kompleksnost sporedne lezije bila manja u usporedbi s istraživanjem *DK-CRUSH IV*.[16,17]

Objavljena su dva bitna dokumenta u području PCI kroničnih potpunih okluzija (CTO). Preporuke *CTO-ARC* namjeravaju standardizirati ključne elemente i definirati postupke, ciljne ishode i dizajn kliničkih istraživanja u području revaskularizacije CTO-a.[18] Drugi je dokument prijedlog stvaranje globalnog algoritma za liječenje CTO-a kojemu je svrha olakšati donošenje odluka i omogućiti edukaciju o PCI CTO-u u

BASKET-SMALL-2 trial investigated 758 patients randomly assigned to drug-coated balloon (DCB) or DES treatment of de novo lesions in vessels ,3 mm diameter. The Kaplan–Meier MACE rate estimate was 15% in both groups [HR=0.99, (95% CI 0.68–1.45); P=0.95]. The study revealed the maintained efficacy and safety of DCB vs. DES in the treatment of de novo coronary small vessel disease up to 3 years.[14] In the context of in-stent restenosis (ISR), the recent DAEDALUS meta-analysis examining DCB-percutaneous transluminal coronary angioplasty vs. DES to treat DES-ISR demonstrated a significantly higher 3-year repeat revascularization rate in the DCB group [HR=1.58, (95% CI 1.16–2.13)].[15]

Complex coronary lesion subsets

The EBC-LM RCT enrolled patients with left main (LM) stenosis involving its bifurcation to a stepwise provisional strategy (n=230) or a systematic dual stent approach (n=237).16The composite endpoint of death, MI, and TLR at 12 months occurred in 14.7% of the stepwise provisional group vs. 17.7% of the systematic dual stent group [HR=0.79, (95% CI 0.5–1.3); P=0.34; **Figure 2**]. Procedure time, X-ray dose, and consumables favoured the stepwise provisional approach. Symptomatic improvement was excellent and equal in each group. These findings support using a stepwise provisional strategy as default for distal LM stem bifurcation PCI, although lower side branch complexity was present compared with the DK-CRUSH IV trial.[16,17]

Two relevant consensus documents in the field of chronic total occlusion (CTO) PCI have been published. The first, the CTO-ARC recommendations, intend to standardize key elements and procedural definitions, endpoint definitions, and clinical trial design principles in the field of revascularization of CTOs.[18] The second is a proposal of a global CTO crossing algorithm aimed to facilitate decision-making and CTO PCI teaching across various geographies and improve the safety, reproducibility, and efficiency of these procedures.[19]

Two registry studies provided contemporary insights into the use and outcomes of atherectomy for calcified lesions. First, an examination of the National Cardiovascular Data Registry (NCDR) CathPCI demonstrated that atherectomy rates tripled in the USA from 1.1% in 2009 to 3.0% in 2016, with a concomitant temporal decline in MACE rates [odds ratio (OR)=0.98, (95% CI 0.97–0.99)] but increase in coronary perforation rates [OR=1.18, (95% CI 1.04–1.35)].[20] In an analysis of 7740 rotational atherectomy procedures from the British Cardiovascular Intervention Society national PCI database, a significant inverse association was observed between atherectomy PCI volume and in-hospital mortality [OR=0.986, (95% CI 0.975–0.996)] as well as MACCE [OR=0.983, (95% CI 0.975–0.993)].[21]

Additional information on the safety and effectiveness of intravascular lithotripsy (IVL) was obtained in the DISRUPT CAD III study, a prospective, single-arm multicentre investigation designed for regulatory approval of coronary IVL, enrolling 431 patients with severely calcified de novo coronary lesions undergoing PCI. At 30-day follow-up, freedom from the MACE was 92.2%; the lower bound of the 95% CI was 89.9%, exceeding a pre-specified performance goal (PG) of 84.4% (P,0.0001). The primary effectiveness endpoint of the proce-

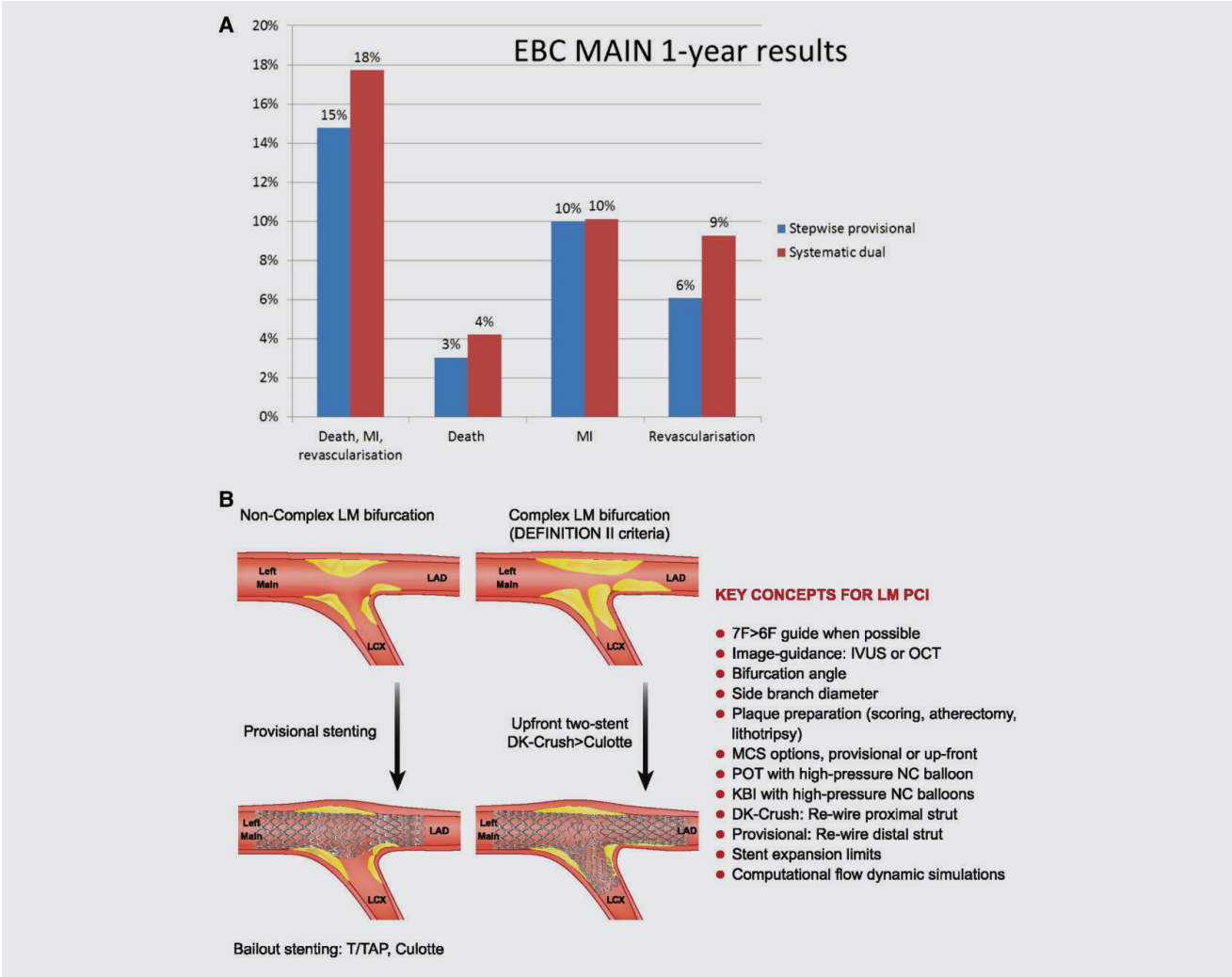

FIGURE 2. Stenting strategies in left main coronary stenoses: (A) primary and secondary endpoints of the EBC-MAIN study and (B) potential strategy for left main bifurcation stenting according to recent trials. Reprinted with permission from (A) Hildick-Smith *et al.* (doi:10.1093/eurheartj/ehab283)[16] and (B) Jaffer *et al.* (doi: 10.1093/eurheartj/ehab363).[17] (from Escaned J, Jaffer FA, Mehilli J, Mehran R. The year in cardiovascular medicine 2021: interventional cardiology. Eur Heart J. 2022 Feb 3;43(5):377-386. doi: 10.1093/eurheartj/ehab884, by permission of OUP on behalf of the ESC).

raznim međunarodnim područjima te i poboljšati sigurnost, ponovljivost i učinkovitost ovih metoda.[19]

Dva su istraživanja dala suvremeni uvid u ishode aterektomije kod kalcificiranih lezija i u njezinu primjenu. U istraživanju iz *National Cardiovascular Data Registry* (NCDR) *CathPCI* utvrđeno je da se učestalost aterektomije utrostručila u SAD-u s 1,1 % tijekom 2009. na 3 % u 2016., uz istodobno vremensko smanjenje učestalosti velikih neželjenih kardiovaskularnih događaja [omjer vjerojatnosti (OR) = 0,98, (95 % interval pouzdanosti 0,97 – 0,99)], ali i uz povećanje učestalosti koronarnih perforacija [omjer vjerojatnosti (OR) = 1,18, (95 % interval pouzdanosti 1,04 – 1,35)].[20] Analiza 7740 aterektomijskih zahvata iz *British Cardiovascular Intervention Society* nacionalne PCI databaze pokazala je inverznu povezanost broja aterektomijskih PCI-ja i unutarbolničkog mortaliteta [omjer vjerojatnosti (OR) = 0,986, (95 % interval pouzdanosti 0,975 – 0,996)], kao i velikih neželjenih kardiovaskularnih i cerebrovaskularnih događaja [omjer vjerojatnosti (OR) = 0,983, (95 % interval pouzdanosti 0,975 – 0,993)].[21]

Dodatne informacije o sigurnosti i učinkovitosti intravaskularne litotripsije donijelo je istraživanje *DISRUPT CAD III*, prospektivna, jednostruka multicentrična studija dizajnirana za odobrenje intravaskularne litotripsije od strane regulato-

ra, koja je uključila 431 bolesnika s teškim kalcificiranim novonastalim lezijama koji su podvrgnuti liječenju primjenom PCI-ja. Nakon praćenja od 30 dana 92,2 % bolesnika bilo je bez velikih neželjenih kardiovaskularnih događaja, donja granica 95 % interval pouzdanosti je bila 89,9 %, nadmašivši ranije postavljeni cilj istraživanja od 84,4 % (P <0,0001). Primarni ishod učinkovitosti uspjeha procedure bio je 92,4 %, donja granica 95 % interval pouzdanosti bila je 90,2 %, što je nadmašilo postavljeni cilj istraživanja od 83,4 % (P <0,0001). [22]

Perkutane koronarne intervencije vođene intrakoronarnom fiziologijom i oslikavanjem

Randomizirana klinička studija *TARGET FFR*, kao dio obnovljenog zanimanja u izvođenju žicom vođene procjene rezultata PCI-ja, istraživala je izvedivost i učinkovitost FFR-om vođene strategije optimizacije u ostvarivanju FFR vrijednosti >0,90 nakon PCI-ja u usporedbi sa standardnom optimizacijom temeljenom na angiografiji.[23] Studija, koja je uključila 260 bolesnika, pokazala je visoku učestalost (68,1 %) FFR vrijednosti >0,90 nakon PCI-ja. U skupini liječenoj FFR-om daljnja intervencija u 30,5 % bolesnika nije znatno povećala udio bolesnika sa završnim FFR-om >0,90, ali je smanjila udio bolesnika sa završnim vrijednostima FFR-a ≤0,80, u usporedbi s grupom vođenom angiografijom [–11,2 %, (95 % interval pouzdanosti –21,87 do 0,35); *P* = 0,045].

Petogodišnji ishodi randomiziranoga kliničkog istraživanja *IVUS-XPL*, koje je uključilo bolesnike s lezijama ≥28 mm podvrgnutim postupku PCI s DES-om, pokazala je smanjenje učestalosti velikih neželjenih kardiovaskularnih događaja u skupini vođenoj intravaskularnim ultrazvukom (IVUS) u usporedbi s onom vođenom samo angiografijom [omjer rizika = 0,50, (95 % interval pouzdanosti 0,34 – 0,75)]. Dobrobit od IVUS-a bila je nastupila smanjenjem učestalosti neuspješne revaskularizacije ciljne lezije.[24]

Rezultati prvoga randomiziranog kliničkog istraživanja *FAVOR III CHINA*, koje je istraživalo dobrobit uporabe funkcionalne koronarne angiografije (bežična, angiografijom izvedena rezerva protoka) za vođenje postupka PCI-ja, izazvali su veliko zanimanje.[25] Ovo placebom kontrolirano istraživanje uključilo je 3825 bolesnika s kroničnim koronarnim sindromom ili AKS-om da bi usporedilo kliničke ishode (velike neželjene kardiovaskularne događaje) strategije kvantitavnog omjera protoka (QFR) (PCI je bila poduzeta ako je QFR bio ≤0,80) i angiografski vođenom strategijom (PCI učinjena na osnovi vizualne angiografske procjene). Nakon jednogodišnjega praćenja učestalost velikih neželjenih kardiovaskularnih događaja bila je 5,8 % i 8,8 % u QFR-om i angiografski vođenoj skupini [omjer rizika = 0,65, (95 % interval pouzdanosti 0,51 – 0,83); *P* = 0,0004].

Visokorizičan nestabilan plak

Nekoliko novih istraživanja pružilo je novi uvid u dijagnozu i intervencijsko liječenje nestabilnih plakova. U analizi 1497 istraživanja bolesnici s koronarnom bolesti srca kojima je ponavljan IVUS tijekom 18 – 24 mjeseci, povećanje IVUS-om zabilježenog prigušenja ili ehogenosti bilo je povezano s većom učestalošću kardiovaskularnih događaja, podupirući potencijalnu ulogu te metode u pronalaženju visokorizičnih nestabilnih plakova.[26] Oslikavanje IVUS-om pružilo je osnovu za preventivno PCI istraživanje *PROSPECT-ABSORB*.[27]

dural success was 92.4%; the lower bound of the 95% CI was 90.2%, which exceeded the PG of 83.4% (P,0.0001).[22]

Percutaneous coronary intervention guidance with intracoronary physiology and imaging

As part of the renewed interest in performing wire-based functional assessment of PCI results, the TARGET FFR RCT investigated the feasibility and efficacy of an FFR-guided optimization strategy in achieving post-PCI FFR values of >0.90, compared with the standard optimization based on angiography.[23] The study, which included 260 patients, demonstrated a high rate (68.1%) of post-PCI FFR values >0.90. In the FFR-guided arm, further intervention in 30.5% patients did not significantly increase the proportion of patients with a final FFR >0.90, but reduced the proportion of patients with a final FFR, ≤0.80, compared with the angiography-guided arm [–11.2%, (95% CI –21.87 to –0.35); P=0.045].

The 5-year outcomes of the IVUS-XPL RCT, which enrolled patients with lesions ≥28 mm undergoing DES PCI, demonstrated a sustained reduction in MACE rates in the IVUS-guided group compared to the angiography-alone group [HR=0.50, (95% CI 0.34– 0.75)]. Benefits of IVUS were driven by reductions in TLR rates.[24]

The results of the first RCT investigating the clinical benefit of using functional coronary angiography (wireless, angiography- derived flow reserve) to guide PCI, FAVOR III China, has generated great interest.[25] This sham-controlled RCT enrolled 3825 patients with chronic coronary syndrome or ACS to compare the clinical outcomes (MACE) of a quantitative flow ratio (QFR) strategy (PCI performed whenever the QFR is ≤0.80) or an angiography-guided strategy (PCI performed based on the visual angiographic assessment). At 1-year follow-up, MACE rate was 5.8 and 8.8% in the QFR- and angio-guided arms, respectively [HR=0.65, (95% CI 0.51–0.83); P=0.0004].

High-risk vulnerable plaque

Several studies provided new evidence on the diagnosis and interventional management of vulnerable plaques. In an analysis of 1497 trials, CAD patients undergoing serial IVUS over 18–24 months, progression of IVUS-detected attenuation or echolucency associated with a higher rate of cardiovascular events, supporting a potential role IVUS identification of high-risk vulnerable plaques.[26] The IVUS imaging further provided the foundation for the preventative PCI PROSPECT-ABSORB trial.[27] Patients (n=185) with lesions with .65% plaque burden were randomized to medical therapy or PCI with the biodegradable drug-eluting ABSORB scaffold. Target lesion failure rates (primary endpoint) were similar in both groups of ~4.4% at 24 months (P=0.96), although the study was not powered for clinical endpoints. The secondary endpoint of the lesion-related MACE trended in favour of the PCI group (P=0.12). Thus, the study provides favourable evidence to support future RCTs on this topic powered to draw conclusive results.

The debate on whether lesion biology, and not its ischaemia-generating character, impacts prognosis has been warmed-up by the results of the COMBINE OCT-FFR study, a prospective, double-blind investigation focused on the management

Bolesnici (n = 185) s lezijama koje su imale >65 % opterećenja plakom bili su raspoređeni u skupinu koja je liječena medikamentnom terapijom i skupinu koja je liječena biorazgradivom ABSORB potpornicom koja oslobađa lijek. Neuspješna revaskularizacija ciljne lezije (primarni ishod) bila je slična u objema skupinama, približno 4,4 % nakon 24 mjeseca (P = 0,96), iako snaga studije nije bila dovoljna za procjenu kliničkih ishoda. Sekundarni ishod, s lezijom povezani veliki neželjeni kardiovaskularni događaj, išao je u prilog skupini koja je liječena primjenom PCI-ja (P = 0,12). Stoga to istraživanje donosi povoljne dokaze koji podupiru buduće randomizirane kliničke studije o spomenutoj temi uz dizajn studije koji će moći rezultirati uvjerljivim zaključcima.

Rasprava o tome utječe li sastav lezije, a ne njezina obilježja ishemije, na prognozu, potaknuta je rezultatima prospektivnog dvostruko slijepog istraživanja *COMBINE OCT-FFR* usredotočenog na liječenje lezija koje nisu odgovorne za AKS u bolesnika sa šećernom bolesti. Kad god je vrijednost FFR-a bila >0,80, postupak PCI odgođen je i učinjena je optička koherentna tomografija da se utvrdi prisutnost ili odsutnost fibroateroma s tankom kapom (TCFA). Naknadno su uspoređeni ishodi bolesnika u kojih je bio prisutan TCFA s bolesnicima u kojih je on bio odsutan.[28] Bolesnici s FFR negativnim i TCFA prisutnim plakom činili su 25 % kohorte i imali su mnogo veću učestalost neželjenih kardiovaskularnih događaja nakon 18 mjeseci u usporedbi s FFR negativnim i TCFA odsutnim plakom [omjer rizika = 4, 65 (95 % interval pouzdanosti 1,99 – 10, 8)], sukladno prije objavljenim rezultatima istraživanja *CLIMA*. Općenito, predvidljivo je da će veća istraživanja o preventivnoj PCI kod visokorizičnih lezija koje su zabilježene intravaskularnim oslikavanjem biti započeta na osnovi navedenih studija.

Transkatetersko liječenje stenoze aortalnog zalistka

Kateterske opcije liječenja aortalnog zalistka dugo su prisutne kao metoda liječenja stenoze tog zalistka. Prošlogodišnje publikacije u navedenom području fokusirale su se na randomizirana kontrolirana istraživanja koja su uspoređivala različite transkateterske biološke zalistke, potom one koja su testirala različite pristupe sa svrhom povećanja sigurnosti transkateterske implantacije aortalnog zalistka (TAVI), dugoročne ishode nakon TAVI-ja ili kirurške zamjene aortalnog zalistka (SAVR) te na ažurirane Smjernice ESC/EACTS 2021. za liječenje bolesti srčanih zalistaka.

Obilježja različitih bioproteza zalistaka

Najnovije generacije balonom širećeg *Sapien* zalistka (BEV) i samoekspandirajućeg *CoreValve Evolute* zalistka (SEV) bile su uspoređene u randomiziranom istraživanju *SOLVE-TAVI* (*compariSon of secOnd generation self-expandable vs. balloon-expandable Valves and gEneral vs. local anesthesia in Transcatheter aortic Valve Implantation*). Navedena dva tipa zalistka imala su slična obilježja nakon jednogodišnjega praćenja što se tiče zajedničkog ishoda sastavljenog od ukupne smrtnosti, moždanog udara, umjerene ili teške paravalvularne regurgitacije i implantacije trajnog elektrostimulatora [HR = 0,94, (95% CI 0,70 – 1,26); P = 0,66].[29]

of ACS non-culprit stenosis in diabetic patients. Whenever the FFR was .0.80, PCI was deferred and an optical coherence tomography was performed to assess the presence or absence of thin- cap fibroatheromas (TCFA). Subsequently, the outcomes of TCFA-positive patients were compared with those of TCFA-negative patients.[28] Patients with FFR-negative TCFA-positive plaques comprised 25% of the cohort, and exhibited significantly higher 18-month MACE rates than those with FFR-negative, TCFA-negative plaques [HR=4.65, (95% CI 1.99–10.8)], consistent with the earlier CLIMA study. Overall, it is foreseeable that larger studies of preventative PCI of high-risk lesions identified by intravascular imaging will be launched based on these studies.

Transcatheter treatment of aortic valve stenosis

The catheter-based aortic valve procedure has long been entered in the treatment armamentarium of aortic valve stenosis. Publications of the last year in this field are focused on RCTs comparing different transcatheter valvular bioprostheses, on testing different approaches to increase the safety of transcatheter aortic valve implantation (TAVI) procedures, long-term outcomes after TAVI or surgical aortic valve replacement (SAVR), as well as the update of 2021 ESC/EACTS Guidelines for the management of valvular heart disease.

Performance of different bioprosthetic valves

The newest generation of balloon-expandable Sapien valve (BEV) and self-expandable CoreValve Evolute valve (SEV) has been randomly compared within the setting of the SOLVE-TAVI (compariSon of secOnd-generation self-expandable vs. balloon-expandable Valves and gEneral vs. local anesthesia in Transcatheter aortic Valve Implantation) trial. These two modern valve systems perform similar regarding the combined endpoint of all-cause mortality, stroke, moderate or severe paravalvular leakage, and permanent pacemaker implantation at 1 year [HR=0.94, (95% CI 0.70–1.26); P=0.66].[29]

In the SCOPE-2 RCT (Safety and Efficacy Comparison of Two TAVI Systems in a Prospective Randomized evaluation-2), the recent generation of SEV was compared with the first-generation ACURATE neo bioprosthesis. In this study of 796 patients, the non-inferiority of ACURATE neo to SEV regarding the 1-year incidence of all-cause death or stroke was not proven (15.8 vs. 13.9%, absolute risk difference 1.8%, upper one-side 95% confidence limit 6.1%; P=0.0549 for non-inferiority). The higher rate of residual moderate or severe aortic regurgitation with the ACURATE neo compared with the SEV (10.0 vs. 3.0%, P=0.002) might have contributed to this result.[30] With the newest generation, ACURATE neo 2 bioprosthesis, the rate of moderate or severe aortic regurgitation is clearly reduced up to 2.5% at 1-year follow-up.[31]

U istraživanju *SCOPE-2* (*Safety and Efficacy Comparison of Two TAVI Systems in a Prospective Randomized evaluation-2*) novija generacija SEV-a uspoređivana je s bioprotezom prve generacije *ACURATE neo*. U tom istraživanju u 796 bolesnika nije dokazana neinferiornost *ACURATE neo* s obzirom na SEV kada se promatrala jednogodišnja incidencija ukupne smrtnosti ili moždanog udara (15,8 % prema 13,9 %, apsolutna razlika rizika 1,8 %, jednostrana 95% granica pouzdanosti 6,1%; P = 0,0549 za neinferiornost). Moguće je da je veći udio zaostale umjerene ili teške aortalne regurgitacije *ACURATE neo* zalistka u usporedbi sa SEV (10,0 % prema 3,0 %, P = 0,002) pridonio ovakvim rezultatima.[30] Najnovija generacija *ACURATE neo 2* bioproteze ima nižu učestalost umjerene ili teške aortne regurgitacije, koja iznosi do 2,5 % u jednogodišnjem praćenju.[31]

Tehnička obilježja sa svrhom poboljšanja sigurnosti transkateterske implantacije aortalnog zalistka

Povećanje iskustva operatera i napredci u TAVI uređajima pridonijeli su smanjenju učestalosti moždanog udara povezanog sa zahvatom, poboljšavajući pritom sigurnost procedure TAVI. S druge strane, „tihe" ishemijske ozljede mozga detektirane primjenom difuzijski ponderirane magnetne rezonancije primijećene su u >80 % bolesnika s TAVI-jem.[32] Radi izbjegavanja klinički značajnih i „tihih" ozljeda mozga, publicirana su dva važna istraživanja u kojima se analizirala dobrobit od uređaja za zaštitu mozga tijekom TAVI procedure. U *REFLECT I (Reduce the Impact of Cerebral Embolic LEsions after TransCatheter Aortic Valve ImplanTation*) randomiziranom istraživanju rabljen je *TriGuard*™ sustav za zaštitu mozga. Od planiranoga broja bolesnika, uključeno je njih samo 68,8 % (n = 258). Primarni je ishod bio „hijerarhijski" skupni ishod sastavljen od ukupne smrtnosti ili moždanog udara nakon 30 dana, kliničkog pogoršanja nakon 2 – 5 dana prema *National Institutes of Health Stroke Scale* ili 30-dnevno pogoršanje prema *Montreal Cognitive Assessment* i ukupni volumen moždane ishemije mjerene difuzijski ponderiranom magnetnom rezonancijom nakon 2 – 5 dana. Nije bilo značajne razlike između skupina ni u primarnome „hijerarhijskom" zajedničkom ishodu (srednji rezultat učinkovitosti, više je bolje: −5,3 ± 99,8 TriGuard prema 11,8 + 96,4 kontrola, P = 0,31) ni u incidenciji „tihih" ozljeda središnjega živčanog sustava.[32] Navedni su rezultati poduprti i sljedećim *REFLECT II* istraživanjem, koje je uključivalo 220 bolesnika (63,4 % od planiranih) randomiziranih u omjeru 2 : 1 u skupinu u kojoj je primjenjivan *TriGuard 3* sustav tijekom TAVI-ja, odnosno u kontrolu skupinu. Unaprijed određen primarni ishod kojim je istraživana superiornost ponovno nije ostvaren (srednji rezultat učinkovitosti, više je bolje: −8,58 TG3 prema 8,08 kontrola, P = 0,857).[33] Rezultati navedenih istraživanja upućuju na selektivno korištenje sustavom za protekciju mozga tijekom TAVI-ja.

Balonska dilatacija [balonska aortalna valvuloplastika (BAV)] prije implantacije zalistka može povećati rizik od puknuća anulusa, embolizacijskih komplikacija i hemodinamske nestabilnosti. Zbog toga bi izbjegavanje navedenog postupka moglo dovesti do pojednostavnjivanja zahvata TAVI i vjerojatnog povećanja sigurnosti. U istraživanju *DIRECTAVI* [*TAVI Without Balloon Predilatation (of the Aortic Valve) SAPIEN 3*] direktni TAVI nasumično je uspoređen s klasičnim pristupom uporabom BAV-a prije ugradnje nove generacije BEV-a.[34]

Technical features to enhance transcatheter aortic valve implantation procedure safety

Increasing operators' experience and advances in TAVI devices led to a decline in peri-TAVI stroke rates, thus, improving the TAVI procedure safety. On the other hand, silent ischaemic brain injury was detected by diffusion-weighted magnetic resonance effects in > 80% of the TAVI patients.[32] Aiming to avoid clinical and silent brain injury, two important RCTs have been published evaluating the performance of cerebral-protection devices during TAVI procedures. In the REFLECT I (Reduce the Impact of Cerebral Embolic LEsions after TransCatheter Aortic Valve ImplanTation) trial, TriGuard™ HDH cerebral-protection device was randomly used during TAVI. Only 68.8% (n=258) of the planned patients were enrolled. The primary efficacy endpoint was a hierarchical composite of all-cause mortality or any stroke at 30 days, National Institutes of Health Stroke Scale worsening at 2–5 days or Montreal Cognitive Assessment worsening at 30 days and total volume of cerebral ischaemic lesions detected by diffusion- weighted magnetic resonance imaging at 2–5 days. Neither the primary hierarchical efficacy endpoint (mean efficacy score, higher is better: −5.3+99.8 TriGuard vs. 11.8+96.4 control, P=0.31) nor the incidence of silent central nervous system injury was significantly different between both treatment strategies.[32] These results were supported by the next REFLECT II trial, which enrolled 220 patients (63.4% of the planned patients) and randomly compared in 2:1 fashion use or not use of the TriGuard 3 embolic protection device during TAVI. Again, the pre-specified primary superiority efficacy endpoint was not met [mean scores (higher is better): −8.58 TG3 vs. 8.08 control; P=0.857).[33] Findings of these studies suggest a selective use of cerebral- protection devices during TAVI.

Balloon dilatation [balloon aortic valvuloplasty (BAV)] prior to valve implantation might increase the risk of annulus rupture, embolization, and haemodynamic instability. Thus, avoiding it might be attractive to simplify the TAVI procedure and probably increase the procedure safety. In the DIRECTAVI [TAVI Without Balloon Predilatation (of the Aortic Valve) SAPIEN 3] trial, direct TAVI without BAV was randomly compared with the conventional strategy using BAV with new-generation BEV.[34] The rate of device success in direct TAVI was non-inferior to that of BAV before the TAVI group [80.2 vs. 75.7%, mean difference 4.5%, (95% CI 4.4– 13.4); P=0.02 for non-inferiority]. Few patients needed an unplanned BAV before TAVI, suggesting an anatomy-related upstream selection of patients in need of BAV before TAVI.[34]

Long-term outcomes after transcatheter aortic valve implantation or surgical aortic valve replacement

Important insights about the long-term comparative performance of TAVI and SAVR among low-risk patients with aortic valve stenosis were derived from the NOTION RCT. In a TAVI population with a mean age of 79.1+4.8 years and a mean STS score of 3.0 +1.7%, the 8-year estimated risks for all-cause mortality (51.8 vs. 52.6%; P=0.90), stroke (8.3 vs. 9.1%; P=0.90),

Učestalost uspješne implantacije u izravnom pristupu pokazala se neinferiornom s obzirom na BAV prije TAVI-ja [80,2 % prema 75,7 %, srednja razlika 4,5 %, (95 % CI 4,4 – 13,4); P = 0,02 za neinferiornost]. Nekolicina bolesnika podvrgnuta je neplaniranom BAV-u prije TAVI-ija, što upućuje na anatomski orijentiranu selekciju bolesnika kojima je potrebna BAV prije TAVI-ja.[34]

Dugoročni ishodi nakon transkateterske implantacije aortalnog zalistka ili njegove kirurške zamjene

Bitan uvid u dugoročna komparativna svojstva TAVI-ja i SAVR-a u bolesnika niskog rizika sa stenozom aortalne valvule pružili su rezultati istraživanja *NOTION*. U skupini bolesnika u kojih je izveden TAVI s prosječnom dobi od 79,1 ± 4,8 godina i srednjim STS-om od 3,0 ± 1,7 %, osmogodišnji rizici sveukupnog mortaliteta (51,8 % prema 52,6 %, P = 0,90), moždanog udara (8,3 % vs. 9,1 %; P = 0,90) ili MI (6,2 % prema 3,8 %; P = 0,33) bili su slični nakon TAVI-ja ili SAVR-a (**slika 3**). Suprotno tomu, rizik od strukturnog propadanja zalistka bio je niži nakon TAVI-a nego nakon SAVR-a (13,9 % prema 28,9 %; P = 0,0017).[35] Budući da je sada TAVI indiciran i za bolesnike niskog rizika s duljim očekivanim trajanjem života, navedeni dugoročni podatci ohrabrujući su za TAVI u pogledu kliničkih ishoda i izdržljivosti zalistka.

Druga kontinuirano rastuća populacija bolesnika s TAVI jesu oni podvrgnuti tom postupku zbog propale kirurške bioproteze. Prvi puta istraživači međunarodnog Registra *VIVID* izvijestili su o osmogodišnjem praćenju bolesnika podvrgnutih zahvatu valvula u valvulu [*„valve-in-valve"* (ViV)]. Preživljenje je bilo dulje u bolesnika s malim propalim biološkim zalistkom nego u onih s većim (33,2 % prema 40,5 %, P = 0,001). Nadalje, neovisnim prediktorima ponovne intervencije nakon ViV zahvata pokazali su se raniji prisutni teški nerazmjer između veličine zalistka i bolesnika, malpozicija zalistka, uporaba balonom širećeg zalistka i bolesnikova dob. Stoga odluka operatera u obama slučajevima – bilo za inicijalni SAVR bilo za ViV zahvat, može znatno utjecati na kliničke ishode.[36]

Što se tiče liječenja stenoze aortalnog zalistka, nove Smjernice ESC/EACTS[37] ističu važnost djelovanja srčanog tima i bolesnika pri odabiru načina liječenja aortalnog zalistka (klasa I., LOE C). Nadalje, uz *STS risc score*, sama životna dob bolesnika sada je preporučena kako neovisni kriterij za donošenje odluke za TAVI ili za SAVR, pri čemu je TAVI preporučen bolesnicima s ≥75 godina (neovisno o opративnom riziku, klasa I., LOE A). Još jedna novost jest preporuka za liječenje aortalnog zalistka u asimptomatskih bolesnika s teškom stenozom aortalnog zalistka i disfunkcijom lijeve klijetke (ejekcijska frakcija lijeve klijetke <50 %) bez drugog uzroka (klasa I., LOE B).

Dodatna farmakoterapija u intervencijskoj kardiologiji

Važna su istraživanja 2021. godine bila publicirana u području antiagregracije terapije nakon PCI-ja. Istraživanje *MASTER DAPT*[38] bilo je prvo otvorenog tipa koje je evaluiralo skraćeno trajanje dvojne antiagregacijske terapije (DAPT) u odnosu prema uobičajenom režimu u bolesnika s visokim rizikom od krvarenja (HBR) podrvgnutih PCI-ju. Između 30. i 45. dana nakon PCI-ja 4579 bolesnika koji nisu doživjeli neželjeni dor MI (6.2 vs. 3.8%; P=0.33) were similar after TAVI and SAVR (Figure 3). Whereas, the risk of structural valve deterioration was lower after TAVI than after SAVR (13.9 vs. 28.3%; P=0.0017).[35] As TAVI now is indicated for low-risk patients with longer life expectancy, these long-term results are reassuring for TAVI in terms of clinical outcomes and valve durability.

Another continuously growing TAVI population is the collective of patients undergoing TAVI for failed surgical bioprosthesis. For the first time, the investigators of the international VIVID registry reported an 8-year follow-up data of patients undergoing Valve-in-Valve (ViV) procedures. Survival was lower among patients with small-failed bioprostheses compared with those with large-failed bioprostheses (33.2 vs. 40.5%, P=0.01). In addition, independent predictors of reinterventions after ViV procedures were pre-existing severe prosthesis–patient mismatch, device malposition, use of balloon-expandable valves, and patients' age. Thus, operator decision during both original SAVR and the ViV procedure might substantially influence clinical outcomes.[36]

Regarding the treatment of aortic valve stenosis, the new ESC/EACTS Guidelines[37] highlight the importance of interaction heart team and patient regarding the aortic valve repair strategy selection (Class I, LOE C). Furthermore, alongside the STS risk score, patient's age alone is now recommended as a determinant factor for TAVI or SAVR selection with TAVI recommended in patients aged ≥75 years (independent of operative risk score; Class I, LOE A). Another novelty is the recommendation of aortic valve repair in asymptomatic patients with severe aortic stenosis and left ventricular dysfunction (left ventricular ejection fraction ,50%) without another cause (Class I, LOE B).

Adjunctive pharmacotherapy in interventional cardiology

Landmark studies have been published this year in the field of antiplatelet therapy after PCI. The MASTER DAPT study[38] was the first open-label RCT evaluating an abbreviated dual antiplatelet therapy (DAPT) duration vs. a standard regimen among patients with high bleeding risk (HBR) undergoing PCI. Between 30 and 45 days after PCI, 4579 event-free subjects were randomly assigned to single antiplatelet therapy (SAPT) with either P2Y12 or aspirin, or to a DAPT for at least 5 additional months (6 months after the index procedure). At 12 months after PCI, the short DAPT strategy was not inferior to the standard DAPT in terms of MACCEs, and was associated with a significant BARC (Bleeding Academic Research Consortium) 2, 3, or 5 bleeding risk reduction [–2.82%, (95% CI –4.40 to –1.24); P,0.001].

In the STOPDAPT-2 ACS trial,[39] patients undergoing PCI for ACS, 1-month DAPT followed by clopidogrel monotherapy for 11 months did not meet the criteria for non-inferiority compared with a 12-month DAPT for the composite of cardiovascular death, MI, stroke, stent thrombosis, thrombolysis in myocardial infarction major or minor bleeding [3.2 vs. 2.8%; HR=1.14, (95% CI 0.80– 1.62); P=0.06]. Secondary outcome analyses revealed a higher incidence of nearly all ischaemic events within the short DAPT group, with only marginal gain in terms of bleeding risk. However, a meta-analysis[40] including 32145 patients from five RCTs confirmed that a DAPT of ≤3 months followed by P2Y12 monotherapy was associated with a 37% relative risk reduction of bleeding [HR=0.63, (95% CI 0.45–0.86); P=0.004] and a similar

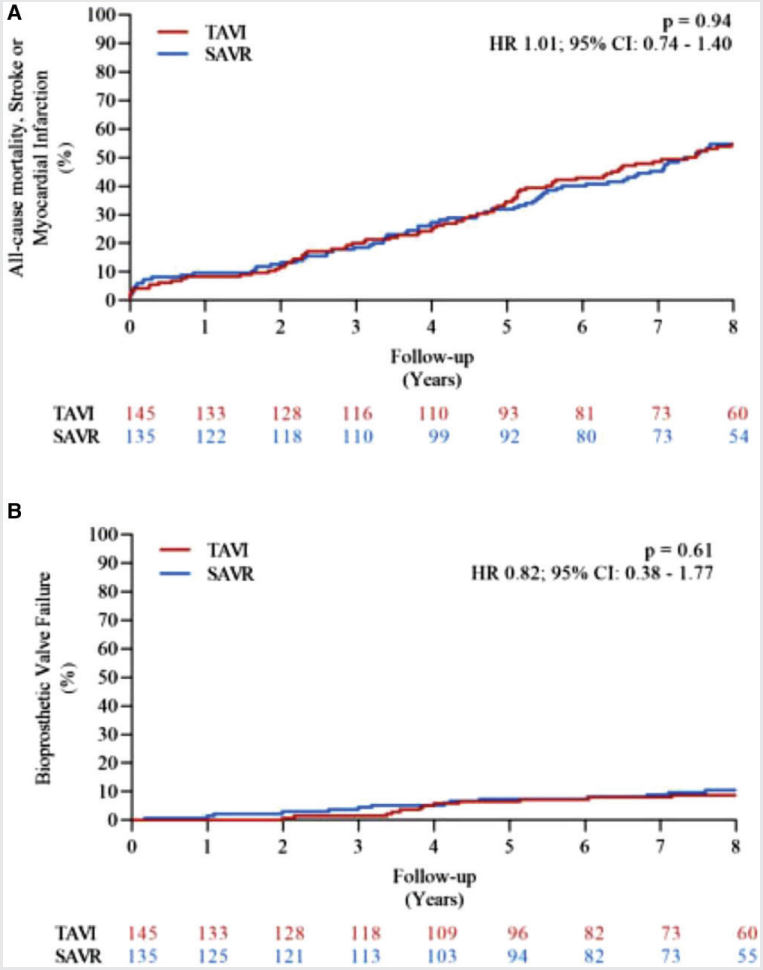

FIGURE 3. Long-term performance of transcatheter aortic valve implantation and surgical aortic valve replacement among low-risk patients with aortic valve stenosis derived from the randomized NOTION trial. (A) Composite endpoint combining all-cause mortality, stroke, or myocardial infarction. (B) Bioprosthetic valve failure. Reprinted with permission from Jørgensen *et al*. (doi:10.1093/eurheartj/ehab375).[35] (from Escaned J, Jaffer FA, Mehilli J, Mehran R. The year in cardiovascular medicine 2021: interventional cardiology. Eur Heart J. 2022 Feb 3;43(5):377-386. doi: 10.1093/eurheartj/ehab884, by permission of OUP on behalf of the ESC).

gađaj, randomizirano je za nastavak liječenja jednim antiagregacijskim lijekom (SAPT), bilo lijekom P2Y12 ili acetilsalicilatnom kiselinom (ASK), ili za nastavak terapije DAPT-om još barem 5 dodatnih mjeseci (6 mjeseci nakon početne procedure). Nakon 12 mjeseci od PCI-ja, terapija kratkog DAPT-a bila je neinferiorna uobičajenom DAPT-u u pogledu MACCE-a, a bila je povezana sa znatnom redukcijom rizika od krvarenja klasificiranog po BARC-u (*Bleeding Academic Research Consortium*) u skupine 2, 3 ili 5 [–2,82 %, (95 % CI – 4,40 do –1,24); P < 0,001].

U istraživanja *STOPDAPT-2 ACS*[39] u bolesnika s AKS-om liječenim primjenom PCI-ja, jednomjesečni DAPT praćen s 11 mjeseci monoterapije klopidogrelom, nije dostigao kriterije neinferiornosti u usporedbi sa standardnom DAPT trajanja 12 mjeseci, kad se gledao zajednički ishod sastavljen od kardiovaskularne smrtnosti, infarkta miokarda, moždanog udara, tromboze stenta, malog ili velikog krvarenja prema TIMI klasifikaciji [3,2 % prema 2,8 %; HR = 1,14, (95 % CI 0,80 – 1,62); P = 0,06]. Analiza sekundarnih ishoda pokazala je veću incidenciju gotovo svih ishemijskih događaja u skupini kratkog DAPT-a, sa samo graničnom dobiti u redukciji krvarećih komplikacija. Međutim, metaanaliza[40] koja je obuhvatila 32 145 bolesnika iz pet randomiziranih istraživanja potvrdila je da je DAPT ≤3 mjeseca uz nastavak P2Y12 monoterapije povezana

s 37 %-tnom redukcijom relativnog rizika krvarenja [HR = 0,63, (95 % CI 0,45 – 0,86); P = 0,004], a uz sličnu učestalost fatalnih ili ishemijskih događaja u bolesnika podvrgnutih PCI-ju uz drugu generaciju DES-a. Nadalje, u dvama prospektivnim istraživanjima u bolesnika s HBR-om podvrgnutih PCI-ju (većinom zbog kroničnoga koronarnog sindroma), kratki DAPT od 1 do 3 mjeseca praćen monoterapijom ASK-om bio je neinferioran u pogledu smrtnosti ili infarkta miokarda, a povezan s nižim rizikom od velikog BARC 3 ili 5 krvarenja, u usporedbi sa skupinom bolesnika koja je uzimala DAPT do 12 mjeseci nakon stratifikacije prema bodovnom sustavu sklonosti.[41,42] U *TWILIGHT-HBR* supstudiji monoterapija tikagrelorom nakon 3 mjeseca DAPT-a rezultirala je sličnim ishemijskim ishodima i velikom apsolutnom redukcijom velikih krvarećih komplikacija (BARC 3 i 5) u usporedbi s produljenim DAPT-om, među bolesnicima s HBR-om liječenima primjenom PCI-ja, od kojih dvije trećine zbog AKS-a bez elevacije ST-segmenta.[43] Navedeni novi dokazi pokazuju da je primjena skraćenog DAPT-a sigurna i učinkovita strategija izbjegavanja krvarećih komplikacija, pogotovo među bolesnicima s HBR-om, ali uz potreban dodatni oprez u bolesnika koji su imali AKS.

Uniformna nevođena deeskalacija DAPT-a s tikagrelora na klopidogrel istraživana je u bolesnika s akutnim infarktom miokarda bez neželjena događaja tijekom prvih mjesec dana nakon PCI-ja u istraživanju *TALOS-AMI*.[44] Deeskalacija je znatno reducirala rizik od ukupnih neželjenih kliničkih događaja tijekom 12 mjeseci [4,6 % prema. 8,2 %, HR = 0,55, (95 % CI 0,40 – 0,76); P = 0,0001] ponajprije zbog redukcije krvarećih komplikacija. U istraživanju *HOST-EXAM*[45] bolesnici podvrgnuti PCI-ju prije 6 do 18 mjeseci, randomizirani su na 24-mjesečnu terapiju održavanja monoterapijom klopidogrelom ili ASK-om. Zajednički ciljni ishod sastavljen od ukupne smrtnosti, nefatalnog infarkta miokarda, moždanog udara, ponovnog prijma zbog AKS-a ili BARC krvarenja 3. ili višeg stupnja, bio je znatno reduciran primjenom klopidogrela [5,7 % prema 7,7 %, HR = 0,73, (95 % CI 0,59 – 0,90); P = 0,0035], usprkos većemu broju smrtnih ishoda.

Što se tiče antitrombotske terapije u bolesnika podvrgnutih TAVI-ju, istraživanje *ATLANTIS*[46] nije uspjelo upozoriti na superiornost pune doze apiksabana u usporedbi s trenutačnom uobičajenom terapijom u bolesnika s indikacijom ili bez indikacije za oralnu antikoagulantnu terapiju (OAC) koji su podvrgnuti uspješnom TAVI-ju, istražujući primarni ishod sastavljen od smrtnog ishoda, moždanog udara, infarkta miokarda, sistemske embolije, intrakardijalne ili valvularne tromboze, duboke venske tromboze/plućne embolije ili velikog krvarenja [18,4 % prema 20,1 %, HR = 0,92, (95% CI 0,73 – 1,16)]. Ovi rezultati, zajedno s onim iz ranijih istraživanja *GALILEO*[47] i *POPular TAVI*[48] upućuju na to da bi antitrombocitna monoterapija trebala ostati standardni terapijski režim kad ne postoji indikacija za DAPT ili sistemsku antikoagulantnu terapiju. U istraživanju ENVISAGE[49], bolesnici u kojih je izveden TAVI s indikacijom za OAC, ponajprije zbog fibrilacije atrija, imali su sličnu (tj. neinferiornu) stopu ukupnih neželjnih kliničkih događaja (uključujući ukupnu smrtnost, infarkt miokarda, ishemijski moždani udar, sistemsku tromboemboliju, trombozu zalistka ili veliko krvarenje) s edoksabanom u usporedbi s antagonistima vitamina K [17,3 prema 16,5 na 100 osoba/godina, HR = 1,05, (95 % CI 0,85 – 1,31), P = 0,93], usprkos većoj incidenciji velikoga krvarenja [9,7 prema 7,0 na 100 osoba/godina, HR = 1,40, (95 % CI 1,03 – 1, 91); P = 0,93 za neinferiornost].

rate of fatal and ischaemic events in patients undergoing PCI with a second-generation DES. Additionally, in two prospective studies of HBR patients undergoing PCI (mainly for chronic coronary syndrome), a short DAPT of 1 or 3 months followed by aspirin monotherapy was non-inferior in terms of death or MI and was associated with a lower incidence of major BARC 3 or 5 bleeding when compared with a historical cohort receiving up to 12-month DAPT after propensity score stratification.[41,42] In the TWILIGHT-HBR substudy, ticagrelor monotherapy after a 3-month DAPT resulted in similar ischaemic outcomes and a large absolute reduction in major BARC 3 or 5 bleeding compared with a prolonged DAPT, among HBR patients undergoing PCI, two-thirds of whom for a non-STE ACS.[43] This new evidence altogether indicates that a short DAPT course is a safe and effective bleeding-avoidance strategy, especially among HBR patients, but extra caution is warranted among those presenting with ACS. A uniform unguided DAPT de-escalation of ticagrelor to clopidogrel was investigated in patients with acute MI and event-free during the first month after PCI in the TALOS-AMI trial.[44] De-escalation significantly decreased the risk of net adverse clinical events up to 12 months [4.6 vs. 8.2%, HR=0.55, (95% CI 0.40– 0.76); P=0.0001] mainly by reducing bleeding complications. In the HOST-EXAM trial,[45] patients who had undergone PCI 6–18 months prior were randomly assigned to a 24-month maintenance therapy with clopidogrel or aspirin monotherapy. The risk of a composite of all-cause death, non-fatal MI, stroke, readmission due to ACS, or BARC bleeding type 3 or greater was significantly reduced with clopidogrel [5.7 vs. 7.7%, HR=0.73, (95% CI 0.59– 0.90); P=0.0035], despite a numerically higher rate of fatalities.

Concerning the antithrombotic treatment in patients undergoing TAVI, the ATLANTIS[46] failed to demonstrate the superiority of a full-dose apixaban when compared with the current standard of care in patients with or without oral anticoagulation (OAC) indication, who have undergone a successful TAVI, with respect to the primary endpoint of death, stroke, MI, systemic emboli, intracardiac or valve thrombosis, deep vein thrombosis/pulmonary embolism, or major bleeding [18.4 vs. 20.1%, HR=0.92, (95% CI 0.73–1.16)]. These results, together with the previous GALILEO[47] and POPular TAVI[48] trials, suggest that the antiplatelet monotherapy should remain the default antithrombotic agent when there is no other indication for DAPT or systemic anticoagulation. In the ENVISAGE study,[49] TAVI patients, with an indication to OAC mainly for atrial fibrillation, experienced similar (i.e. non-inferior) net adverse clinical events (including death from any cause, MI, ischaemic stroke, systemic thromboembolism, valve thrombosis, or major bleeding) with edoxaban when compared with vitamin K antagonists [17.3 vs. 16.5 per 100 person/years, HR=1.05, (95% CI 0.85–1.31), P=0.93], despite a higher incidence of major bleeding [9.7 vs. 7.0 per 100 person/years, HR=1.40, (95%CI 1.03–1.91); P=0.93 for non-inferiority].

Final outlook

The evidence reported over the last year in the field of interventional cardiology discussed in this review will likely be reflected in upcoming clinical practice guidelines and trigger new studies. Ongoing studies in functional coronary angiography[50] will complement the disruptive evidence provided by the FAVOR III China trials. The growing interest in integrating plaque biology and ischaemic burden to predict outcomes of

Zaključno stajalište

Dokazi koji su izneseni tijekom prošle godine u području intervencijske kardiologije prokomentirani u ovome pregledom članku vjerojatno će se odraziti na buduće kliničke smjernice i potaknuti nove studije. Istraživanja koja su u tijeku s područja funkcionalne koronarne angiografije[50] dopunit će „uznemirujuće" dokaze iz istraživanja *FAVOR III China*. Rastući interes intrigantne biologije plaka i ishemijsko opterećenje u predviđanju ishoda bolesnika sa stenozama koronarnih arterija zasigurno će potaknuti daljnje rasprave i istraživanja. Velika istraživanja u području transkateterskog liječenja strukturnih bolesti srca, osim TAVI-ja, očekuju se u bližoj budućnosti.[51]

patients with coronary stenosis will surely trigger debates and further research. Major studies on transcatheter structural heart interventions other than the TAVI are expected in the near future.[51]

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