

# Godina 2019. u kardiologiji: koronarne intervencije

## The year in cardiology: coronary interventions The year in cardiology 2019

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### Uvod

Istraživanja na polju perkutanih koronarnih intervencija (PCI) fokusiraju se na optimizaciju strategija liječenja, razvoj nove opreme i farmakoterapije sa svrhom poboljšanja ishoda te identifikacije bolesnika koji su pod visokim rizikom i koji će imati dobit od novih metoda liječenja koje ciljaju na razvoj aterosklerotskih promjena. Tijekom protekle godine objavljene su važne kliničke studije čija je svrha bila istražiti uspješnost različitih strategija liječenja i vrsta stentova u bolesnika s opstruktivnom bolesti koronarnih arterija (CAD). Osim toga, objavljene su smjernice koje daju preporuke za liječenje ovakvih bolesnika. Svrha je ovoga članka dati pregled rezultata značajnih studija objavljenih tijekom 2019. te raspraviti o njihovu utjecaju na kliničku praksu.

### Revaskularizacija bolesnika nakon srčanog zastoja ili akutnoga koronarnog sindroma

Istraživanje *Coronary Angiography after Cardiac Arrest* značajna je studija koja je promijenila

### Preamble

Percutaneous coronary intervention (PCI) research focuses on the optimization of treatment strategies, the development of novel equipment and pharmacotherapies for improved results, and on risk stratification and identification of high-risk patients that will benefit from emerging therapies targeting atherosclerotic evolution. Over the last year, important clinical studies have been reported that examined the efficacy of different treatment strategies and stent platforms in patients with obstructive coronary artery disease (CAD) and guidelines have been published to provide recommendations about the management of these patients. The aim of this article is to summarize the findings of the pivotal studies published in 2019 and discuss their impact on clinical practice.

### Revascularization in patients with cardiac arrest or acute coronary syndromes

Coronary Angiography after Cardiac Arrest (COACT) is a landmark study that changed

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zbrinjavanje bolesnika hospitaliziranih sa srčanim zastojeom nakon uspješno provedene reanimacije, a koji nisu imali infarkt miokarda s elevacijom ST-segmenta (STEMI).<sup>1</sup> U ovom prospektivnom multicentričnom istraživanju, 552 bolesnika primljena s izvanbolničkim arestom s inicijalnim ritmom koji je moguće defibrilirati, a nisu imali očit nekardijalni uzrok srčanog zastoja, randomizirana su na hitnu koronarnu angiografiju i, ako je to bilo potrebno, revaskularizaciju ili odgođenu koronarografiju nakon neurološkog oporavka. Akutna trombotska okluzija nađena je kod samo 3,4 % bolesnika u skupini podvrgnutoj hitnoj koronarografiji, te u 7,6 % bolesnika u skupini odgođene koronarografije. Nije bilo statistički značajne razlike među randomiziranim skupinama bolesnika u preživljenju nakon otpusta (65,2 % nasuprot 68,7 %), a ni nakon 90 dana (64,5 % nasuprot 67,2 %). Osim toga, nije bilo razlike u incidenciji kombiniranog ishoda preživljenja bez neurološkog deficita, odnosno s blagim ili srednje teškim neurološkim deficitom (62,9 % nasuprot 64,4 %). Ovi su rezultati u suprotnosti s ranijim opservacijskim istraživanjima koja penaliziraju odgođenu koronarografiju te podupiru oba pristupa.

Suprotno tomu, u istraživanju *Complete vs. Culprit-Only Revascularization Strategies to treat Multivessel Disease after Early PCI for STEMI* (COMPLETE) potvrdila se vrijednost agresivnoga pristupa revaskularizaciji u bolesnika sa STEMI-jem.<sup>2</sup> U tom je istraživanju 4041 bolesnik koji je imao višezilnu CAD randomiziran u omjeru 1 : 1 na potpunu revaskularizaciju ili revaskularizacije samo vodeće lezije s pomoću PCI-ja. Nakon 3 godine praćenja incidencija kombiniranog ishoda smrti zbog kardiovaskularne bolesti ili infarkta miokarda (MI) bila je niža u bolesnika koji su podvrgnuti potpunoj revaskularizaciji u usporedbi s bolesnicima u kojih je učinjena samo PCI vodeće lezije (7,8 % nasuprot 10,5 %;  $P = 0,004$ ). Valja napomenuti da je korist od potpune revaskularizacije bila slična u bolesnika u kojih je tijekom inicijalne hospitalizacije učinjena potpuna revaskularizacija i onih u kojih je to učinjeno u drugoj hospitalizaciji unutar 45 dana od otpusta, uz dodatnu napomenu da se ova usporedba ne temelji na randomiziranom uzorku, već je odluka o terminu potpune revaskularizacije prepuštena operaterima. Ishodi potpune revaskularizacije u bolesnika s NSTEMI-jem za sada još nisu potpuno istraženi.

## Kronični koronarni sindromi

### Revaskularizacija nasuprot farmakološkom liječenju

Unatoč opsežnim dokazima koji podupiru potpunu revaskularizaciju u bolesnika hospitaliziranih zbog STEMI-ja, studije koje ispituju vrijednost PCI-ja u poboljšanju ishoda u bolesnika s kroničnim koronarnim sindromom pokazuju neujednačene rezultate. Retrospektivna analiza koja je uključivala 16 029 bolesnika s nalazom oslikavanja perfuzije miokarda pozitronskom emisijom kompjutoriziranom tomografijom pokazala je da rana kirurška ili perkutana revaskularizacija u bolesnika s ishemijskim opterećenjem >5 – 10 % poboljšava prognozu.<sup>3</sup> Ovi rezultati, međutim, nisu potvrđeni u *post hoc* analizi istraživanja *Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation* (COURAGE) koje je uključivalo 1379 bolesnika s nalazom perfuzijskog oslikavanja u opterećenju uz nalaz kvantitativne koronarne angiografije.<sup>4</sup> Nakon 7,9 godina praćenja opsežnost CAD-a koja je definirana brojem zahvaćenih koronarnih žila, a ne intenzitetom ishemijske, bila je prediktor preživljenja. Perkutana koronarna intervencija u ovoj kohorti nije poboljšala ishode u usporedbi

the management of patients admitted with a cardiac arrest who had successful resuscitation and no ST elevation myocardial infarction (STEMI).<sup>1</sup> In this prospective multicentre trial, 552 patients admitted with an out of hospital cardiac arrest with an initial shockable rhythm who did not have an obvious non-cardiac cause of arrest were randomized to immediate coronary angiography and if needed coronary revascularization or delayed coronary angiography after neurological recovery. An acute thrombotic occlusion was noted only in 3.4% of the patients in the immediate angiography and in 7.6% of the patient in the delayed angiography group. Survival rate at discharge (65.2% vs. 68.7%) and at 90-day follow-up (64.5% vs. 67.2%) was not different between randomization groups. In addition, there was no difference for the incidence of the composite endpoint survival with good cerebral performance or mild or moderate disability (62.9% vs. 64.4%). These findings contradict previous observational studies that penalized a delayed invasive assessment of the coronary artery anatomy and justify both approaches in this setting.

Conversely, the Complete vs. Culprit-Only Revascularization Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) study confirmed the value of an aggressive revascularization strategy in patients admitted with a STEMI.<sup>2</sup> In this study, 4041 patients who had multivessel CAD were randomized in a 1:1 ratio to complete revascularization vs. culprit-lesion-only PCI. At 3-year follow-up, the incidence of the composite endpoint cardiovascular death or myocardial infarction (MI) was lower in patients undergoing complete revascularization as compared to the patients that had PCI only in the culprit vessel (7.8% vs. 10.5%;  $P = 0.004$ ); of note, the benefit of complete revascularization was similar in patients who had an in-hospital second procedure compared to a procedure following readmission within 45 days post-discharge; however, this comparison was not randomized, as the choice for timing of the second procedure was left to operator's discretion. The prognostic value of complete revascularization in patients with non-STEMI has not been fully investigated yet.

## Chronic coronary syndromes

### Revascularization vs. medical therapy

Despite the robust evidence supporting the prognostic implications of complete revascularization in patients admitted with a STEMI, studies examining the value of PCI in improving outcomes in patients with a chronic coronary syndrome show mixed results. A retrospective analysis including 16 029 patients who had positron emission computed tomography myocardial perfusion imaging demonstrated that an early surgical or percutaneous revascularization was associated with improved prognosis in patients with an ischaemic burden >5–10%.<sup>3</sup> These findings, however, were not confirmed in a *post hoc* analysis of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial that included 1379 patients who had stress perfusion imaging and quantitative coronary angiography.<sup>4</sup> At 7.9 years of follow-up, the extent of CAD—defined by the number of the diseased vessels—and not the severity of ischaemia was a predictor of survival. Percutaneous coronary intervention in this cohort did not improve outcomes over optimal medical therapy; more importantly, there was no

s optimalnom medikamentnom terapijom. Nije bilo interakcija između opširnosti ishemijske ili terapijskoga pristupa CAD (konzervativni nasuprot PCI-ju).

U skladu s ovim rezultatima istraživanja *International Study of Comparative Health Effectiveness With Medical And Invasive Approaches* (ISCHEMIA) koje je uključivalo 5179 bolesnika sa srednje teškom ili teškom ishemijskom na neinvazivnim metodama oslikavanja, a bili su randomizirani na optimalnu medikamentnu terapiju ili optimalnu medikamentnu terapiju i PCI, nije pokazana razlika u kombiniranom ishodu (smrtnost zbog kardiovaskularnih bolesti, infarkta miokarda, hospitalizacije zbog nestabilne angine, simptoma zatajivanja srca ili srčanog zastoja s uspješnim oživljavanjem) između skupina nakon 3,3 godine praćenja (15,5 % nasuprot 13,8 %,  $P = 0,34$ ).<sup>5</sup> U spomenutom istraživanju primjena PCI-ja bila je povezana s poboljšanjem kvalitete života, smanjenjem anginoznih simptoma te nižom incidencijom spontanog infarkta miokarda (HR 0,67; 95 % CI 0,53 – 0,83;  $P < 0,01$ ). Važno ograničenje istraživanja ISCHEMIA jest visoka učestalost (28 %) prijelaza iz konzervativne u invazivnu skupinu, što je moglo utjecati na prikazane rezultate. Analiza „as-treated“ nije zasa- da još uvijek objavljena.

Povezanost između prisutnosti vijabilnog miokarda, kirurške revaskularizacije i kliničkih ishoda nedavno je analizirana u *post hoc* analizi istraživanja *Surgical Treatment for Ischaemic Heart Failure* (STICH).<sup>6</sup> Ta analiza koja je uključivala 601 bolesnika koji su imali ejijsku frakciju lijeve klijetke  $\leq 35$  % i procjenu vijabilnosti. Istraživanje nije uspjelo dokazati utjecaj prisutnosti ili odsutnosti vijabilnosti miokarda na preživljenje u bolesnika koji su podvrgnuti kirurškoj revaskularizaciji nakon 10,4 godine praćenja. Istraživanje *REVAvascularization for Ischaemic VEntricular Dysfunction* (REVIVED) NCT01920048 trenutno se provodi te istražuje sigurnosti i učinkovitost PCI-ja u poboljšanju ishoda u bolesnika sa zatajivanjem srca.

## Podskupine bolesnika i lezija

### *Bolest debila lijeve koronarne arterije i trožilna koronarna bolest srca*

Optimalna strategija revaskularizacije u bolesnika s uznapredovalom CAD (tj. trožilnom koronarnom bolesti srca ili bolesti debila lijeve koronarne arterije /LM/) i u bolesnika s dijabetesom razmotrena je u Smjernicama Europskoga kardiološkog društva (ESC) za revaskularizaciju miokarda iz 2018. godine: kirurška je revaskularizacija trenutno metoda izbora u dijabetičara s višezilnom koronarnom bolešću, dok PCI ima II. B razinu indikacije u bolesnika s rezultatom na SYNTAX bodovnoj ljestvici  $\leq 22$  i nije preporučena u bolesnika sa SYNTAX zbrojem  $>22$ .<sup>7</sup>

Ove se preporuke temelje na rezultatima istraživanja *Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease* (FREEDOM) koja je uključivala 1900 dijabetičara s višezilnom CAD koji su bili randomizirani na kiruršku ili perkutanu revaskularizaciju te su pokazali višu učestalost mortaliteta nakon 8 godina praćenja u PCI skupini u usporedbi sa skupinom koja je bila podvrgnuta kirurškoj revaskularizaciji (24,3 % nasuprot 18,3 %,  $P = 0,010$ ).<sup>8</sup> Suprotno tim rezultatima, istraživanje *Synergy between PCI with Taxus and Cardiac Surgery* (SYNTAX) *Extended Survival study* koje je uključilo 1689 bolesnika

interakcija između opširnosti ishemijske ili terapijskoga pristupa CAD (konzervativni nasuprot PCI-ju).

In line with these findings, the International Study Of Comparative Health Effectiveness With Medical And Invasive Approaches (ISCHEMIA study) that included 5179 patients, with moderate or severe ischaemia in non-invasive imaging, who were randomized to optimal medical therapy or optimal medical therapy plus PCI demonstrated no differences in outcomes between groups at 3.3 years of follow-up for the composite endpoint of cardiovascular death, MI, admission for unstable angina, heart failure symptoms, or resuscitated cardiac arrest (15.5% vs. 13.8%,  $P = 0.34$ ).<sup>5</sup> In this study, PCI was associated with an improvement in the quality of life, a reduction in the angina symptoms and a lower incidence of spontaneous MI [hazard ratio (HR) 0.67, 95% confidence interval (CI) 0.53–0.83;  $P < 0.01$ ]. An important limitation of the ISCHEMIA study is the high (28%) crossover rate from the conservative to the invasive arm which may have affected the reported results; the as-treated analysis has not been reported yet.

The association between the presence of viable myocardium, surgical revascularization, and clinical outcomes was recently evaluated by a *post hoc* analysis of the Surgical Treatment for Ischaemic Heart Failure (STICH) study.<sup>6</sup> This analysis, that included 601 patients who had a left ventricular ejection fraction  $\leq 35$ % and viability assessment, failed to demonstrate an impact of the presence or absence of myocardial viability on the survival benefit noted in patients undergoing surgical revascularization at 10.4-year follow-up. The REVAvascularisation for Ischaemic VEntricular Dysfunction (REVIVED) study (NCT01920048) is currently examining the safety and efficacy of PCI in improving prognosis in patients with heart failure.

## Patient and lesion subset

### *Left main and three-vessel disease*

The optimal revascularization strategy in patients with advanced CAD [i.e. three-vessel disease or left main stem (LMS) disease] and in diabetic patients has been discussed in the 2018 European Society of Cardiology (ESC) Guidelines on myocardial revascularization: surgical revascularization is currently the recommended treatment strategy in diabetic patients with multivessel CAD, while PCI has a IIB indication in patients with a SYNTAX score  $\leq 22$  and is not recommended in patients with SYNTAX score  $>22$ .<sup>7</sup>

These recommendations are in line with the findings of the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) Follow-On study that included 1900 diabetic patients with multivessel disease that were randomized to surgical or percutaneous revascularization and reported a higher mortality rate at 8 years of follow-up in the PCI arm compared to the surgical revascularization group (24.3% vs. 18.3%,  $P = 0.010$ ).<sup>8</sup> Conversely, the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) Extended Survival study that included 1689 patients with LMS or three-vessel disease did not demonstrate differences in the all-cause mortality between patients allocated to PCI and those treated surgically at 10 years of follow-up (27% vs. 24%,  $P = 0.092$ ). There was, however, a treatment effect by subgroup inter-

s LM-om ili trožilnom CAD nije pokazalo razlike u smrtnosti zbog svih uzroka između bolesnika liječenih PCI-jem i onih liječenih kirurškom revaskularizacijom nakon 10 godina praćenja (27 % nasuprot 24 %,  $P = 0,092$ ). Unatoč tomu, postojala je interakcija učinka liječenja u podskupini ovisno o prisutnosti i odsutnosti trožilne CAD; smrtnost je bila povećana u PCI podskupini u usporedbi sa skupinom liječenom aortokoronarnim premoštenjem (CABG) (HR 1,41; 95 % CI 1,10 – 1,80), dok navedena razlika nije postojala u bolesnika s bolešću LM (HR 0,90; 95 % CI 0,68 – 1,20). Suprotno tomu, nije bilo razlike u ishodima između dviju strategija liječenja u dijabetičara i nedijabetičara ( $P$  za interakciju 0,660).<sup>9</sup> Ograničenje obaju istraživanja jest u tome da je u bolesnika liječenih PCI-jem primjenjivan stent koji luči lijek (DES) 1. generacije, a koji se ne upotrebljava u modernoj praksi, te u činjenici da su oba istraživanja analizirala samo ukupnu smrtnost, a ne i ishode specifične za kardiovaskularna istraživanja.

Istraživanje *Evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL)* zaobišlo je prije spomenuta ograničenja. U tom je istraživanju 1905 bolesnika s bolešću LM i SYNTAX zbrojem  $\leq 32$  randomizirano na PCI s drugom generacijom DES-a ili CABG.<sup>10</sup> U skupini liječenoj PCI-jem intravaskularni ultrazvuk (IVUS) raobljen je u 77,2 % bolesnika.<sup>11</sup> Nakon pet godina praćenja nije bilo razlike između skupina u kombiniranom ishodu koji je uključivao ukupnu smrtnost, MI i moždani udar (22,0 % u PCI skupini nasuprot 19,2% u CABG skupini;  $P = 0,13$ ). Učestalost neželjenih događaja nakon 30 dana praćenja bila je niža u PCI skupini (4,9 % nasuprot 8,0 %), nije bilo razlike između skupina u razdoblju između 30 dana i 1 godine (4,1 % nasuprot 3,8 %), dok je u razdoblju od 1 do 5 godina praćenja zabilježena viša stopa neželjenih događaja u skupini liječenoj s pomoću PCI-ja (15,1 % nasuprot 9,7 %). Bolesnici randomizirani na CABG bili su skloniji razvoju neželjenoga cerebrovaskularnog događaja (5,2 % nasuprot 3,3 %), dok su oni liječeni PCI-jem imali višu učestalost ukupne smrtnosti (13,0 % nasuprot 9,9 %) te su češće bili podvrgnuti revaskularizaciji zbog razvoja ishemijske (16,9 % nasuprot 10 %). Slično onomu što je utvrđeno u SYNTAX studiji, nakon 3 i 5 godina praćenja nije bilo razlike u ishodima između dviju strategija liječenja u dijabetičara i u onih koji nisu dijabetičari.<sup>10,12</sup>

### Perkutana koronarna intervencija na bifurkacijskim stenozama

Tijekom 2019. godine objavljeni su rezultati trogodišnjega praćenja ispitanika iz istraživanja DKCRUSH V. Slično rezultatima koji su objavljeni nakon jedne godine praćenja, tehnika „double kiss-crush“ bila je povezana s nižom učestalošću revaskularizacija ciljne lezije (TLR, 5,0 % nasuprot 10,3 %,  $P = 0,029$ ), infarkta ciljne žile (1,7 % nasuprot 5,8 %,  $P = 0,017$ ) te definitivne ili vjerojatne tromboze stenta (0,4 % nasuprot 4,1 %,  $P = 0,006$ ) u usporedbi s privremenim T-stentiranjem.<sup>13</sup> Tehnika „double kiss-crush“ zahtjevnija je procedura i zahtijeva vještinu i stručnost te, s obzirom na navedeno, rezultati istraživanja DKCRUSH V možda ne mogu biti reproducirani u centrima s manje iskusnim operaterima. Nedavno objavljeni 14. konsenzus dokument Europskoga bifurkacijskog kluba, podržava uporabu tehnike privremenog T-stentiranja u liječenju bifurkacijskih lezija te predlaže strategiju dva stenta samo u lezijama s kompleksnom anatomijom, kada je pristup sporednom ogranku zahtjevan ili kada postoji bolest u ostijalnom segmentu koja se proteže  $>5$  mm od karine i/ili sadržava veći

action according to the presence or absence of three-vessel disease; mortality was increased in the PCI group compared to the coronary artery bypass graft (CABG) arm (HR 1.41, 95% CI 1.10–1.80), while there was no differences between the two groups in patients with LMS disease (HR 0.90, 95% CI 0.68–1.20); conversely, there was no difference in outcomes for the two treatment strategies in diabetic and non-diabetic patients ( $P$ -for interaction 0.660).<sup>9</sup> A limitation of both studies is the fact that the patients in the PCI arm were treated with a 1st generation drug-eluting stent (DES) that is not currently used in contemporary practice, and the fact that they both reported only all-cause mortality instead of patient-orientated cardiovascular endpoints.

The Evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) study overcame these limitations; in this study, 1905 patients with LMS disease and SYNTAX score  $\leq 32$  were randomized to PCI with a 2nd generation DES or CABG.<sup>10</sup> In the PCI arm, intravascular ultrasound (IVUS) imaging was used in 77.2% of the cases.<sup>11</sup> At 5-year follow-up, there were no differences between groups for the combined endpoint of all-cause death, MI, or stroke (22.0% in the PCI arm vs. 19.2% in the CABG group;  $P = 0.13$ ). The event rate at 30-day follow-up was lower in the PCI arm (4.9% vs. 8.0%), there was no difference between groups for the period 30 days to 1 year (4.1% vs. 3.8%), while for the period 1–5 years of follow-up a higher event rate was reported in patients undergoing PCI (15.1% vs. 9.7%). Patients randomized to CABG were more likely to suffer a cerebrovascular event (5.2% vs. 3.3%), while those treated with PCI had increased all-cause mortality (13.0% vs. 9.9%) and more often ischaemia driven revascularization (16.9% vs. 10.0%). Similarly to what it has been reported in the SYNTAX study, there was no difference in the outcomes between the two treatment strategies in diabetic and non-diabetic patients at 3- and 5-year follow-up.<sup>10,12</sup>

### Percutaneous coronary intervention of bifurcation stenoses

In 2019, the 3-year follow-up data of the DKCRUSH V study were published; similar to what has been reported at 1-year follow-up, double kiss-crush technique was associated with a lower incidence of target lesion revascularization (TLR, 5.0% vs. 10.3%,  $P = 0.029$ ) target vessel MI (1.7% vs. 5.8%,  $P = 0.017$ ), and definite or probable stent thrombosis (0.4% vs. 4.1%,  $P = 0.006$ ) compared to provisional T-stenting.<sup>13</sup> Double kiss-crush technique, however, is a challenging procedure and requires skills and expertise; therefore, considering that the findings of the DKCRUSH V study may not be reproduced by centres with less experienced operators, the recently published 14th consensus document from the European Bifurcation Club advocates the use of provisional T-stenting technique for the treatment of bifurcations lesions and proposes a two stent strategy only in lesions with a complex anatomy, when access to the side branch is challenging, or when there is ostial disease in the side branches extending  $>5$  mm from the carina and/or increased calcification.<sup>14</sup> In the case of a two stent strategy, the European Bifurcation Club recommends the use of culotte or TAP technique and when the crush technique is considered it proposes the use of the double kiss-crush.

postotak kalcifikacije.<sup>14</sup> U slučaju strategije s dvama stentovima, Euroski bifurkacijski klub preporučuje primjenu „cullotte“ tehnike ili TAP tehnike, a u slučajevima kada se razmatra upotreba „crush“ tehnike, preporučuje „double-kiss crush“ tehniku.

### Liječenje kroničnih totalnih okluzija

EuroCTO klub objavio je 2019. zajednički dokument koji nudi sažet pregled trenutačno dostupnih dokaza (slika 1), razmatra trenutačne indikacije za revaskularizaciju kronične totalne okluzije (CTO), prikazuje unaprjeđenja u opremi za CTO te daje preporuke za trening za izvođenje postupka PCI CTO.<sup>15</sup> U skladu s ESC smjernicama za revaskularizaciju miokarda te uzimajući u obzir rezultate randomiziranih kontroliranih istraživanja, EuroCTO klub preporučuje revaskularizaciju CTO-a ako su prisutni simptomi unatoč optimalnoj medikamentnoj terapiji. U asimptomatskih bolesnika preporučuje se procjena ishemijskog opterećenja te potom revaskularizacija CTO-a ako se dokaže ishemijsko opterećenje ( $\geq 10\%$  mase lijeve klijetke). Ove su preporuke sukladne rezultatima nedavno provedenog istraživanja *Drug-Eluting Stent Implantation vs. Optimal Medical Treatment in Patients With Chronic Total Occlusion (DECISION-CTO)*.<sup>16</sup> U tom je istraživanju 815 bolesnika s CTO-om randomizirano u omjeru 1 : 1 na potpunu revaskularizaciju ili na liječenje drugih opstruktivnih (non-CTO) lezija. Samo četvrtina bolesnika uključenih u dvije skupine imala je jednožilnu bolest. Nakon četiri godine praćenja nije bilo razlike među skupinama u kombiniranom ishodu koji je uključivao smrtnosti, MI, moždani udar ili revaskularizaciju (22,4 % nasuprot 22,3 %,  $P = 0,86$ ), a ni u kvaliteti života. Ovakvi rezultati upućuju na to da u slučajevima višezilne CAD prioritet treba biti u revaskularizaciji non-CTO lezija te u procjeni opširnosti ishemijske prije razmatranja rekanalizacije CTO lezije. Ograničenja navedenog istraživanja, najvećeg ove vrste, bila su u velikoj učestalosti (19,6 %) prelaženja bolesnika iz non-CTO PCI skupine u CTO-PCI skupinu unutar prvih nekoliko dana nakon randomizacije, kao i u činjenici da istraživanje nije bilo dovoljne statističke snage za procjenu primarnog ishoda jer je regrutacija bolesnika prekinuta ranije zbog sporog porasta stope uključenih bolesnika.

### Male koronarne arterije i restenoza u stentu

PCI malih žila povezana je s većom učestalosti velikih neželjenih kardiovaskularnih događaja (MACE) i TLR zbog restenoze u stentu. U godini 2019. provedena je i objavljena unaprijed definirana podanaliza istraživanja *Biodegradable Polymer and Durable Polymer Drug-eluting Stents in an All Comers Population (BIO-RESORT)* koja je uspoređivala ishode nakon PCI-ja na malim žilama ( $< 2,5$  mm) koristeći se ultratankim kobalt krom biorazgradivim polimernim stentovima koji luče sirolimus (potporanj debljine 71  $\mu\text{m}$ ) ili vrlo tankim platina krom biorazgradivim polimernim stentovima koji luče everolimus (potporanj debljine 78  $\mu\text{m}$ ) ili pak ranijom generacijom

### Treatment of chronic total occlusions

In 2019, the EuroCTO Club published a consensus document that summarizes the current evidence (Figure 1), discusses the indications for chronic total occlusion (CTO) revascularization, presents the advances in CTO equipment, and provides recommendations about training in CTO PCI.<sup>15</sup> In line with the ESC guidelines on myocardial revascularization and taking into account the findings of randomized controlled studies, the EuroCTO Club recommends CTO recanalization in the presence of symptoms despite optimal medical therapy; in asymptomatic patients, ischaemic burden assessment is recommended and CTO revascularization is advised if there is evidence of increased ischaemic burden ( $\geq 10\%$  of the left ventricular mass). These recommendations are in line with the findings of the recently reported Drug-Eluting Stent Implantation vs. Optimal Medical Treatment in Patients With Chronic Total Occlusion (DECISION-CTO) trial.<sup>16</sup> In this study, 815 patients with a CTO were randomized in 1:1 ratio to complete revascularization or to the treatment of the obstructive non-CTO lesions whenever these were present. Only one-fourth of the patients included in the two groups had a single-vessel disease. At 4-year follow-up, there was no difference between the two groups for the combined endpoint of death, MI, stroke, or revascularization (22.4% vs. 22.3%,  $P = 0.86$ ) or patients' quality of life. These findings indicate that in case of multivessel disease revascularization of the non-CTO lesion and re-evaluation of the extent of ischaemia and patient symptoms should be considered before advocating recanalization of a CTO. Limitations of the study—the largest of its kind—included the high crossover rate (19.6%) from the non-CTO PCI group to the CTO-PCI group within the first days from randomization as well the fact that it was underpowered for the primary endpoint as patient recruitment was early terminated because of a slow enrolment rate.

### Small vessel and in-stent restenosis

Percutaneous coronary intervention in small vessels has been associated with a higher incidence of major adverse cardiovascular events (MACE) and TLR due to in-stent restenosis. In 2019, a pre-specified sub-analysis of the Biodegradable Polymer and Durable Polymer Drug-eluting Stents in an All Comers Population (BIO-RESORT) study was published that compared outcomes following PCI in small vessels ( $< 2.5$  mm) using ultrathin-strut cobalt chromium biodegradable polymer sirolimus-eluting stents (strut thickness 71  $\mu\text{m}$ ) or very thin-strut platinum chromium biodegradable polymer everolimus-eluting stents (strut thickness 78  $\mu\text{m}$ ) or previous-generation thin strut cobalt-chromium durable polymer zotarolimus-eluting stents (strut thickness 102  $\mu\text{m}$ ). A higher incidence of TLR was noted in the thicker strut zotarolimus-eluting stent than the ultrathin-strut sirolimus-

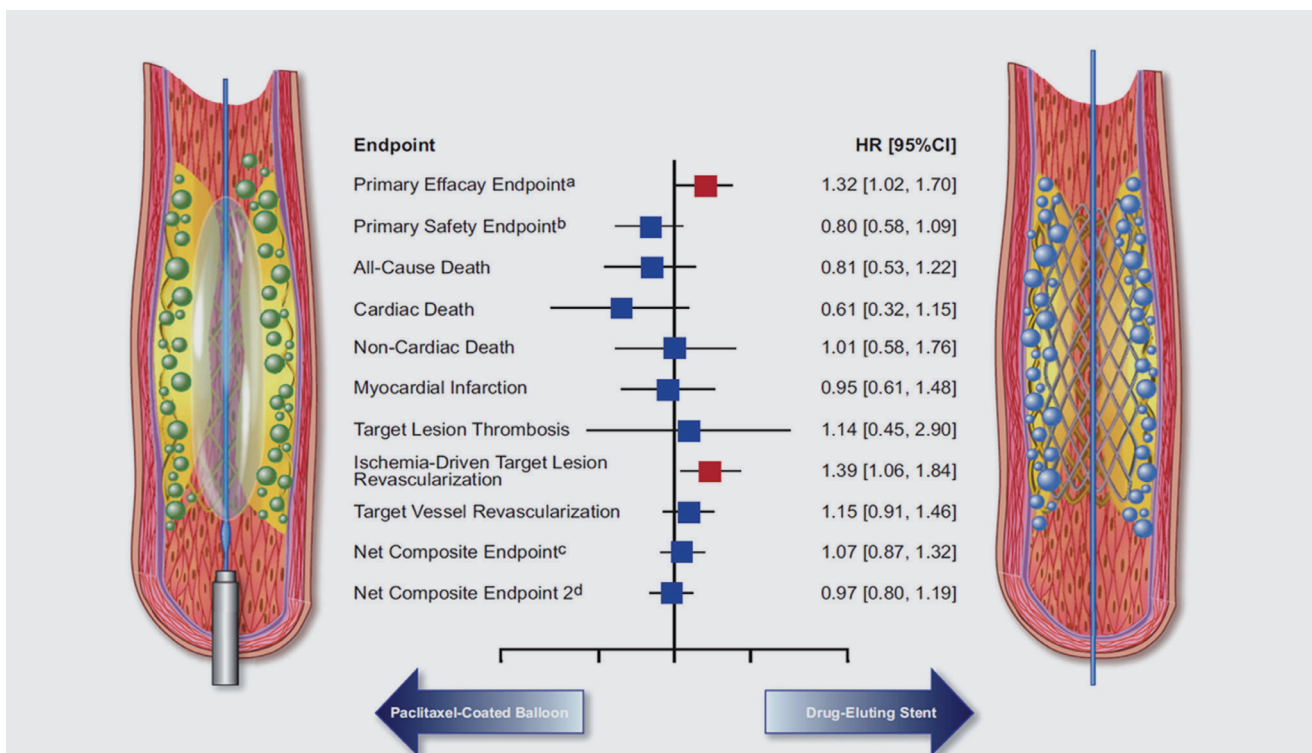
FIGURE 1. Please see the original article (Eur Heart J. 2020 Jan 14;41(3):394-405.).

tankih kobalt krom izdržljivih stentova koji luče zotarolimus (potporanj debljine 102  $\mu\text{m}$ ). Veća incidencija TLR-a zabilježena je u debljim stentovima koji luče zotarolimus u usporedbi s ultratankim stentovima koji luče sirolimus (5,3 % nasuprot 2,1 %,  $P = 0,006$ ), a nije bilo razlike između stentova koji luče everolimus i onih koji luče zotarolimus (4,0 % nasuprot 5,1 %,  $P = 0,31$ ).<sup>17</sup> Ovakvi rezultati uvjerljivo upućuju na prognostičku važnost debljine potporna u stentovima kod malih žila u eri DES-a te su sukladni s prijašnjim istraživanjima koja prikazuju ishode pri uporabi običnih metalnih stentova (BMS).<sup>18</sup>

Restenoza u stentu najčešći je uzrok neuspjeha implantacije stenta. Njezino je liječenje izazovno te je povezano s lošom prognozom i visokom stopom TLR-a.<sup>19</sup> Dvije najučinkovitije strategije liječenja koje se danas primjenjuju jesu balonska angioplastika balonom obloženim lijekom ili implantacija DES-a. U 2019. objavljena je metaanaliza *Difference in Anti-restenotic Effectiveness of Drug-eluting stent and drug-coated balloon* (DAEDALUS) koja je uključivala 1976 bolesnika liječenih balonom obloženim paklitaxelom ili DES-om.<sup>20</sup> Nakon tri godine praćenja angioplastika primjenom balona obloženog paklitaxelom bila je povezana s većom učestalosti TLR-a u usporedbi s implantacijom DES-a (HR 1,32, 95 % CI 1,02 – 1,70;  $P = 0,035$ ), no treba napomenuti da među skupinama nije bilo razlike u kombiniranom ishodu smrti, MI-ja ili tromboze ciljane lezije (slika 2).

eluting stent group (5.3% vs. 2.1%,  $P = 0.006$ ), while there was no difference in the TLR rate between the everolimus and zotarolimus-eluting stent groups (4.0% vs. 5.1%,  $P = 0.31$ ).<sup>17</sup> These findings convincingly highlight the prognostic implications of strut thickness in small vessels in the DES era and are in line with previous studies reporting outcomes in bare-metal stents.<sup>18</sup>

In-stent restenosis represents the most common cause of stent failure; its treatment is challenging and is associated with poor prognosis and a high TLR rate.<sup>19</sup> The two most effective treatment strategies today are drug-coated balloon angioplasty or DES implantation. In 2019, the Difference in Anti-restenotic Effectiveness of Drug-eluting stent and drug-coated balloon AngioPlasty for the occurrence of coronary in-Stent restenosis (DAEDALUS) patient-level meta-analysis was published that included 1976 patients treated with a paclitaxel-coated balloon or a DES.<sup>20</sup> At 3-year follow-up, paclitaxel-coated balloon angioplasty was associated with a higher incidence of TLR comparing to DES implantation (HR 1.32, 95% CI 1.02–1.70;  $P = 0.035$ ); however, there was no difference between groups for the combined endpoint of death, MI, or target lesion thrombosis (Figure 2).



**FIGURE 2.** Summary of the efficacy of paclitaxel-coated balloon angioplasty vs. drug-eluting stent implantation for the treatment of patients with in stent restenosis. Image obtained with permission from Giacoppo et al.<sup>20</sup> <sup>a</sup>Primary efficacy endpoint: target lesion revascularization. <sup>b</sup>Primary safety endpoint: the composite of death, myocardial infarction, or target lesion thrombosis. <sup>c</sup>Net composite endpoint: the composite of death, myocardial infarction, target lesion thrombosis, or target lesion revascularization. <sup>d</sup>Net composite endpoint: the composite of death, myocardial infarction, target lesion thrombosis, or target vessel revascularization. This content is covered by the terms of the CC BY-NC 4.0 Open Access agreement.

## Postojeći i novi intervencijski uređaji

### Lijekom obloženi stentovi i bioresorbiljive skele

Smjernice ESC-a za revaskularizaciju miokarda preporučuju primjenu druge generacije DES-a u svakodnevnoj kliničkoj praksi.<sup>7</sup> Produljeno praćenje ispitanika iz istraživanja *Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-elevation Myocardial Infarction* (COMFORTABLE-AMI) i analiza intravaskularnog oslikavanja, koji su objavljeni ove godine pružili su dodatne dokaze o superiornosti DES-a u usporedbi s BMS-om u hospitaliziranih bolesnika sa STEMI-jem. Nakon 5 godina praćenja implantacija Biolimus stentova povezana je s nižom učestalošću infarkta ciljne lezije (2,2 % nasuprot 5,0 %,  $P = 0,02$ ) i TLR vođenog ishemijskom (4,4 % nasuprot 10,4 %,  $P < 0,001$ ) u usporedbi s BMS-om.<sup>21</sup>

Istraživanje BIOSTEMI fokusiralo se na liječenje bolesnika sa STEMI-jem, a randomiziralo je 1300 ispitanika na ugradnju ultratankih kobalt krom stentova koji luče sirolimus nasuprot trajnim polimernim stentovima koji luče everolimus. Nakon 12 mjeseci praćenja liječenje ultratankim stentovima koji luče sirolimus bilo je povezano s nižom incidencijom neuspjeha tretiranja ciljne lezije (TLF – *target lesion failure*) u usporedbi sa stentovima koji luče everolimus (4 % nasuprot 6 %; omjer stopa 0,59; 95 % Bayesian interval pouzdanosti 0,37 – 0,94; vjerojatnost superiornosti 0,986).<sup>22</sup> Suprotno tomu, istraživanje TALENT koje je uspoređivalo ishode u svih bolesnika randomiziranih na ultratanke kobalt krom stentove koji luče sirolimus i trajne polimerne stentove koji luče everolimus nije pokazala razliku u incidenciji kombiniranih ishoda kardiovaskularne smrtnosti, infarkta ciljne lezije i klinički indicirane TLR između skupina (4,9 % nasuprot 5,3 %,  $P$  za neinferiornost  $< 0,0001$ ).<sup>23</sup>

Bioresorbiljive skele uvedene su kako bi se zaobišla ograničenja DES-a i poboljšali dugoročni ishodi. Međutim, povećana učestalost neželjenih događaja prijavljena pri uporabi ovih stentova tijekom kratkoročnog i srednjoročnog praćenja izazvale su zabrinutost oko njihove sigurnosti te danas oni nisu preporučeni za rutinsku kliničku uporabu. Nedavna metaanaliza randomiziranih istraživanja koje su uspoređivale Absorb bioresorbiljive vaskularne skele (BVS) i stentove koji luče everolimus pokazala je veću incidenciju TLF-a u Absorb BVS nakon 5 godina praćenja (14,9 % nasuprot 11,6 %,  $P = 0,030$ ), što je bilo pripisano većoj incidenciji infarkta ciljne lezije i TLR-a vođena ishemijskom.<sup>24</sup> Važna je analiza pokazala veću učestalost ovih događaja u razdoblju do 3. godine praćenja, međutim, tijekom praćenja od 3. do 5. godine incidencija kardiovaskularne smrti, MI ciljne lezije, ishemijskom vođenog TLR-a i tromboze stenta bila je slična između skupina u bolesnika koji nisu imali neželjenih događaja tijekom početne 3 godine praćenja. Ovi rezultati prvi put daju jedinstveni uvid o vremenu nastupa neželjenih događaja nakon ugradnje bioresorbiljivih skela te upućuju na nisku stopu događaja u dugoročnom praćenju nakon njihove potpune resorpcije.

### Pomoćni intervencijski uređaji

Intravaskularna litotripsija (IVL) pojavila se tijekom posljednjih nekoliko godina kao učinkovita alternativa za liječenje kalcificiranih lezija koje su povezane s povećanim rizikom od razvoja komplikacija i lošijom prognozom.<sup>25</sup> Ova metoda uključuje plasiranje katetera s balonom na vrhu u kojemu se nalazi više odašiljača koji generiraju zvučne valove te potom selektivno frakturiraju vaskularni kalcij, a pritom ne utječu

## Existing and emerging interventional devices

### Drug-eluting stents and bioresorbable scaffolds

The ESC Guidelines on myocardial revascularization recommends the use of 2nd generation DES in daily clinical practice.<sup>7</sup> The extended follow-up of the Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE-AMI) study and the nested intravascular imaging analysis published this year has provided further evidence about the superiority of DES over bare-metal stents in patients admitted with a STEMI. At 5-year follow-up, Biolimus stent implantation was associated with a lower incidence of target vessel MI (2.2% vs. 5.0,  $P = 0.02$ ) and ischaemia driven TLR (4.4% vs. 10.4%,  $P < 0.001$ ) than treatment with a bare-metal stent.<sup>21</sup>

The BIOSTEMI study also focused on the treatment of patients with STEMI and randomized 1300 subjects to ultrathin cobalt chromium sirolimus-eluting stent vs. durable polymer everolimus-eluting stent implantation. At 12-month follow-up, treatment with ultrathin sirolimus-eluting stents was associated with a lower incidence of target lesion failure (TLF) than everolimus-eluting stents (4% vs. 6%; rate ratio: 0.59, 95% Bayesian credibility interval: 0.37–0.94; posterior probability of superiority 0.986).<sup>22</sup> Conversely, the TALENT study that compared outcomes in all-comer patients randomized to ultrathin cobalt chromium sirolimus-eluting stent and durable polymer everolimus-eluting stent failed to show a difference for the incidence of the composite endpoint of cardiac death, target-vessel MI, or clinically indicated TLR between groups (4.9% vs. 5.3%,  $P_{\text{for non-inferiority}} < 0.0001$ ).<sup>23</sup>

Bioresorbable scaffolds have been introduced to overcome the limitations of DES and improve long-term outcomes. However, the increased event rate reported in these devices at short- and intermediate-term follow-up raised concerns about their safety and today are not recommended for routine clinical use. A recent meta-analysis of randomized studies comparing the Absorb bioresorbable vascular scaffold (BVS) and the everolimus-eluting stent showed a higher incidence of TLF in the Absorb BVS at 5-year follow-up (14.9% vs. 11.6%,  $P = 0.030$ ) that was attributed to a higher incidence of target vessel MI and ischaemia driven TLR.<sup>24</sup> Landmark analysis demonstrated a higher event rate in the Absorb BVS group for the period 0–3 years of follow-up; however, for the period 3–5 years of follow-up, the incidence of cardiac death, target vessel MI, ischaemia driven TLR, and device thrombosis was similar between groups in patients who had not experienced an event in the first 3 years. These findings for the first time provide unique insights about the timing of the events in bioresorbable scaffolds and indicate a low event rate at long term after their full resorption.

### Adjunctive interventional devices

Intravascular lithotripsy (IVL) has emerged over the last years as an effective alternative for the treatment of calcified lesions that are associated with an increased risk of complications and worse prognosis.<sup>25</sup> It involves the advancement of a catheter with a balloon on its tip that contains multiple emitters which generate sonic pressure waves that selectively fracture vascular calcium without affecting the integrity of the fibroelastic tissue of the plaque.<sup>26</sup> The Shockwave

na integritet fibroelastičnoga tkiva samog plaka.<sup>26</sup> Istraživanje *The Shockwave Coronary Rx Lithoplasty Study* (DISRUPT CAD) bilo je prvo koje je sustavno istraživalo sigurnost i efikasnost IVL-a u 60 bolesnika s izrazito kalcificiranim lezijama i duljinom  $\leq 32$  mm. Procedura je bila uspješna pri svim lezijama te je rezultirala akutnim dobitkom 1,7 mm i postproceduralnim postotkom smanjenja dijametra stenoza za 12,2 %. Cjelokupna stopa MACE-a nakon 6 mjeseci praćenja bila je 8,3 %. Prijavljena su 3 periproceduralna MI-ja i dvije kardiovaskularne smrti.<sup>27</sup> Slični su rezultati dobiveni i u DISRUPT CAD II istraživanju koje je uključivalo 120 bolesnika. U tom istraživanju stopa unutar bolničkog MACE-a bila je 5,8 % (7 non-Q wave MI), dok je nakon 30 dana praćenja stopa porasla na 7,6 %. Optička koherentna tomografija (OCT) provedena je u 48 bolesnika prije i 47 nakon postavljanja stenta te je pokazala da je IVL uzrokovala  $3,4 \pm 2,6$  fraktura po leziji te rezultirala akutnim dobitkom od  $4,79 \pm 2,45$  mm<sup>2</sup> i odličnom ekspanzijom stenta od  $102,8 \pm 30,6$  %.<sup>28</sup> Nedavno su Wilson *et al.*<sup>29</sup> pokazali da je IVL terapija povezana s ventrikulskom ektopijom i asinkronom elektrostimulacijom. U ovom istraživanju nisu prijavljene maligne aritmije. Istraživanje DISRUPT CAD III koje je u tijeku trebala bi pružiti dodatne dokaze o sigurnosti i učinkovitosti IVL-a u liječenju kalcificiranih lezija (NCT03595176).

## Dodatna farmakoterapija

Vrsta i trajanje antiagregacijske terapije u bolesnika nakon PCI-ja jest područje intenzivnih istraživanja. Studija *Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention* (TWILIGHT) bila je dizajnirana kako bi procijenila optimalnu duljinu dvojne antiagregacijske terapije (DAPT) nakon PCI u bolesnika s visokim rizikom od krvarenja.<sup>30</sup> U tom je istraživanju randomizirano 7119 bolesnika na DAPT tijekom 3 mjeseca, a potom na liječenje samo tikagrelorom ili DAPT-om do 12 mjeseci. Kratkotrajna DAPT bila je povezana s nižom učestalošću krvarenja (stopa krvarenja prema Bleeding Academic Research Consortium; BARC klasifikacija); tip 2, 3 i 5 krvarenja je bio 4,0 % u skupini s kratkotrajnom DAPT nasuprot 7,1 % u skupini koja je primala DAPT 12 mjeseci,  $P < 0,001$ ). U ovoj studiji nije bilo razlike među skupinama u incidenciji kombiniranog ishoda smrti, MI-ja i moždanog udara.

Suprotno ovim rezultatima, *post hoc* analiza istraživanja *Global Leaders* koje je uključivalo 4570 bolesnika koji su bili podvrgnuti kompleksnoj PCI pokazala je da skupina koja je bila na terapiji acetilsalicilatnom kiselinom (ASK) tijekom 1 mjeseca i potom tikagrelorom 24 mjeseca ima nižu incidenciju primarnog ishoda smrti i MI-ja nakon 2 godine praćenja u usporedbi s konvencionalnom DAPT tijekom 12 mjeseci, a potom ASK kao monoterapija (3,51 % nasuprot 5,43 %;  $P = 0,002$ ). Valja napomenuti da nije bilo razlike među skupinama u riziku od krvarenja (incidencija krvarenja tipa BARC 3 ili 5 bila je 2,45 % nasuprot 2,54 %,  $P = 0,834$ ). Ovi su rezultati potvrđeni analizom na razini bolesnika 8 randomiziranih kontroliranih istraživanja koja su uključivala 14 963 bolesnika, a pokazala je da je u bolesnika s niskim rizikom od krvarenja (*PREdicting bleeding Complications in patients undergoing stent implantation and SubsequEnt Dual ANtiPLatelet Therapy* score  $< 25$ ) produžena DAPT bila povezana s nižom incidencijom ishemijskih događaja, pogotovo u bolesnika koji su podvrgnuti kompleksnoj PCI. Nasuprot tomu, dugotrajna DAPT u bolesnika s visokim rizikom od krvarenja nije reducirala rizik od ishemijskih događaja, a povećala je rizik od krvarenja.<sup>31</sup>

Coronary Rx Lithoplasty Study (DISRUPT CAD) was the first study that systematically examined the safety and efficacy of IVL in 60 patients with heavily calcified lesions and length  $\leq 32$  mm; the procedure was successful in all the lesions resulting in an acute gain of 1.7 mm and a post-procedural percent diameter stenosis of 12.2%. The overall MACE rate at 6 months of follow-up was 8.3%; three peri-procedural MI and two cardiac deaths were reported.<sup>27</sup> Similar were the findings of the DISRUPT CAD II study that included 120 patients; in that study, the in-hospital MACE rate was 5.8% (7 non-Q wave MI), while at 30-day follow-up, the MACE rate was 7.6%. Optical coherence tomography (OCT) imaging was performed in 48 patients before and in 47 after stenting and demonstrated that IVL caused  $3.4 \pm 2.6$  fractures per lesion resulting in an acute gain of  $4.79 \pm 2.45$  mm<sup>2</sup> and an excellent stent expansion of  $102.8 \pm 30.6$ %.<sup>28</sup> Recently, Wilson *et al.*<sup>29</sup> showed that IVL therapy is associated with ventricular ectopics and asynchronous pacing. In this study, no malignant arrhythmias were reported; the ongoing DISRUPT CAD III study is expected to provide further evidence about the safety and efficacy of IVL in the treatment of calcified lesions (NCT03595176).

## Adjunctive pharmacotherapy

The type and the duration of antiplatelet therapy in patients undergoing PCI is an area of intensive research. The Ticagrelor with Aspirin or Alone in High-Risk Patients after Coronary Intervention (TWILIGHT) study was designed to examine the optimal duration of dual antiplatelet therapy (DAPT) following PCI in high bleeding risk patients.<sup>30</sup> The study randomized 7119 patients to DAPT therapy for 3 months and then treatment with ticagrelor monotherapy or DAPT for 12 months. Short duration DAPT was associated with a lower incidence of bleeding [rate of Bleeding Academic Research Consortium (BARC) type 2, 3, and 5 bleeding: 4.0% in the short duration DAPT group vs. 7.1% in the group receiving DAPT for 12 months,  $P < 0.001$ ], while there was no difference between groups in the incidence of the composite endpoint death, MI, or stroke.

Conversely, a *post hoc* analysis of the Global Leaders study including 4570 patients undergoing complex PCI demonstrated that the experimental regimen of aspirin for 1 month and ticagrelor for 24 months was associated with a lower incidence of the primary endpoint death, MI at 2 years of follow-up compared to conventional DAPT for 12 months and then aspirin monotherapy (3.51% vs. 5.43%;  $P = 0.002$ ). Of note, there was no difference between groups in the risk of bleeding (incidence of BARC type 3 or 5 bleeding: 2.45% vs. 2.54%;  $P = 0.834$ ). These findings were confirmed by a patient-level analysis of eight randomized control trials including 14 963 patients which demonstrated that in low bleeding risk patients (*PREdicting bleeding Complications in patients undergoing stent Implantation and SubsequEnt Dual AntiPlatelet Therapy* score  $< 25$ ) prolonged DAPT therapy was associated with a lower incidence of ischaemic events especially in patients undergoing complex PCI. Conversely, long-term DAPT in high bleeding risk patients did not reduce the risk of ischaemic events and increased the risk of bleeding.<sup>31</sup>

Patients suffering from atrial fibrillation undergoing PCI are at increased risk of bleeding as they receive a combination of antiplatelet and anticoagulation therapy. The optimal treatment of these patients has been extensively investigated by



Bolesnici s fibrilacijom atriya koji su podvrgnuti PCI-ju pod povećanim su rizikom od krvarenja jer dobivaju kombinaciju antikoagulantne i antiagregacijske terapije. Optimalno liječenje takvih bolesnika opsežno je istraživano u više velikih randomiziranih kontroliranih istraživanja tijekom nekoliko proteklih godina. Studija AUGUSTUS koja je objavljena ove godine bila je multicentrično randomizirano istraživanje s dizajnom 2 x 2 koje je randomiziralo 4614 bolesnika s fibrilacijom atriya koji su liječeni primjenom PCI-ja uz terapiju P2Y12 inhibitorom i apiksabanom ili antagonistom vitamina K i na acetilsalicilatnu kiselinu ili placebo tijekom 6 mjeseci.<sup>32</sup> Uključeni su bolesnici primali standardnu terapiju u prvim danima nakon PCI-ja jer je randomizacija provedena 6 dana (interkvartilni raspon od 3 do 10 dana) nakon intervencije. Incidencija velikih ili klinički značajnih malih krvarenja bila je viša u bolesnika koji su primali antagoniste vitamina K nego u onih koji su liječeni apiksabanom (14,7 % nasuprot 10,5 %,  $P < 0,001$ ). Bolesnici na apiksabanu imali su nižu učestalost smrtnog ishoda i rehospitalizacije od skupine liječene antagonistima vitamina K (23,5 % nasuprot 27,4 %,  $P = 0,002$ ) uz sličnu incidenciju ishemijskih događaja. Suprotno tomu, acetilsalicilatna kiselina nije imala utjecaja na ove ishode.

Slične je rezultate pokazalo i istraživanje ENTRUST-AF PCI koje je uključilo 1506 bolesnika s fibrilacijom atriya koji su bili liječeni s pomoću PCI-ja da bi se istražile učinkovitost i sigurnost kombinacije P2Y12 inhibitora u kombinaciji s endoksabanom nasuprot kombinaciji DAPT s antagonistom vitamina K.<sup>33</sup> Uključeni su bolesnici randomizirani na dvije skupine otprilike 45 sati nakon PCI-ja. Nije bilo razlike između skupina glede učestalosti velikih krvarenja, klinički značajnih malih krvarenja ili u incidenciji kombiniranog ishoda od kardiovaskularne smrti, moždanog udara, embolije, MI-ja i definitivne tromboze stenta nakon 12 mjeseci praćenja. Metaanaliza randomiziranih kontroliranih studija koja je istraživala sigurnost i učinkovitost dvojne nasuprot trojnoj antiagregacijskoj terapiji u bolesnika s fibrilacijom atriya koji su liječeni metodom PCI-ja objavljena je ove godine te je potvrdila ranije rezultate pokazujući nižu učestalost krvarenja (13,4 % nasuprot 20,8 %,  $P < 0,0001$ ), ali veći rizik od trombozu stenta (1% nasuprot 0,6%,  $P = 0,040$ ) u bolesnika na dvojnoj antiagregacijskoj terapiji.<sup>34</sup>

## Alati za invazivnu dijagnostiku

### Koronarna fiziologija

Nedavna su istraživanja pokazala da frakcijska protočna rezerva (FFR – eng. *fractional flow reserve*) te indeksi odmora (*resting indices*), uključujući trenutačni omjer slobodnog vala (iwFR) imaju vrijednost ne samo u vođenju revaskularizacije nego i u procjeni konačnih rezultata i ishoda nakon PCI-ja.<sup>35,36</sup> Postoje, međutim, povremene razlike između hiperemijskog FFR-a i indeksa odmora. Nekoliko istraživanja u 2019. godini pokušalo je istražiti fiziološke osobitosti lezija s proturječnim nalazima FFR-a i iwFR-a te identificirati vrstu lezija i podskupinu bolesnika u kojih bi metoda izbora bila FFR ili iwFR.<sup>37,38</sup> Nedavna podanaliza istraživanja *Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization* (DEFINE-FLAIR) koja je uspoređivala ishode u bolesnika s lezijom u LAD čija je revaskularizacija odgođena na temelju rezultata FFR-a ili iwFR-a pokazala nižu učestalost neželjenih događaja u skupini iwFR nakon jedne godine praćenja. Navedeno je pripisano nižoj stopi incidencije neplanirane revaskularizacije (2,22 % nasuprot 4,99 %,  $P = 0,03$ ).<sup>39</sup> Suprotno ovim

several large scale randomized control studies over the last years. The AUGUSTUS trial published this year was a multi-centre randomized study with a 2 x 2 factorial design that randomized 4614 patients with atrial fibrillation undergoing PCI to treatment with a P2Y12 inhibitor, and apixaban or vitamin K antagonist, and to aspirin or placebo for 6 months.<sup>32</sup> The recruited patients received standard of care antithrombotic therapy the first days post-PCI as randomization to study groups was performed 6 (interquartile range 3–10) days post-intervention. The incidence of major or clinically relevant non-major bleeding was higher in patients receiving vitamin K antagonist than those treated with apixaban (14.7% vs. 10.5%,  $P < 0.001$ ) and in those treated with aspirin than those receiving placebo (16.1% vs. 9.0%,  $P < 0.001$ ). Patients on apixaban had a lower incidence of death or hospitalization than the vitamin K antagonist group (23.5% vs. 27.4%,  $P = 0.002$ ) and a similar incidence of ischaemic events. Conversely, aspirin did not have an effect to these endpoints.

Similar were the findings of the ENTRUST-AF PCI study which investigated in 1506 patients with atrial fibrillation undergoing PCI the safety and efficacy of the combination of a P2Y12 inhibitor plus edoxaban against the combination DAPT plus vitamin K antagonist.<sup>33</sup> The recruited patients were randomized to the two study groups ≈45 h post-PCI. There was no difference between groups in the incidence of major bleeding-clinically relevant non-significant bleeding or the incidence of the composite endpoint of cardiovascular death, stroke, systemic embolic events, MI, and definite stent thrombosis at 12 months of follow-up. A meta-analysis of randomized controlled trials investigating the safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation undergoing PCI, published this year, confirmed the above findings demonstrating a lower incidence of bleeding (13.4% vs. 20.8%;  $P < 0.0001$ ) but a higher risk of stent thrombosis (1% vs. 0.6%;  $P = 0.040$ ) in patients receiving dual therapy.<sup>34</sup>

## Invasive diagnostic tools

### Coronary physiology

Recent studies have shown that the fractional flow reserve (FFR) and the resting indices including the instantaneous wave free ratio (iwFR) have a value not only in guiding revascularization but also in assessing the final results post-PCI and predicting prognosis.<sup>35,36</sup> There are however occasional discordances between hyperaemic FFR and resting indices. Several studies this year attempted to examine the physiological characteristics of lesions with discordant FFR and iwFR and identify lesion types and subgroup of patients where FFR should be preferred to iwFR and vice versa.<sup>37,38</sup> A recent sub-analysis of the Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularization (DEFINE-FLAIR) study comparing outcomes in patients with a lesion in the left anterior descending coronary artery deferred from revascularization based on the FFR or iwFR estimations showed a lower event rate in the iwFR group at 1-year follow-up that was attributed to a lower incidence of unplanned revascularizations (2.22% vs. 4.99%,  $P = 0.03$ ).<sup>39</sup> Conversely, a *post hoc* analysis of the same study in diabetic patients showed no differences in outcomes between the FFR and iwFR groups (7.2% vs. 10.0%;  $P = 0.30$ ); however, the inci-

rezultatima, *post hoc* analiza istog istraživanja u dijabetičara nije pokazala razlike u ishodima između FFR i iwFR skupina (7,2 % nasuprot 10,0 %,  $P = 0,30$ ). Međutim, učestalost infarkta miokarda koji nije uzrokovao smrtni ishod bila je viša u iwFR skupini (4,7 % nasuprot 1,9 %,  $P = 0,05$ ) uz značajnu interakciju za prisutnost dijabetesa ( $P = 0,04$ ).<sup>40</sup>

Usporedo s uvođenjem indeksa odmora za procjenu funkcijske težine srednje teških lezija, trud je uložen u dizajniranje računalnih metodologija koje bi mogle naknadnom obradom snimaka koronarografije ili drugih invazivnih metoda oslikavanja izračunati FFR. U 2019. predstavljena su dva nova pristupa za računalni izračun FFR-a. Prvi se temelji na tro-dimenzionalnoj kvantitativnoj koronarografiji kao osnovi za izračun geometrije krvnih žila i na procjeni pada tlaka preko lezije, dok se drugi temelji na procesiranju podataka oslikavanja dobivenih OCT-om. Druga metoda omogućuje kombiniranu morfološku i fiziološku procjenu aterosklerotskih lezija te procjene rezultata nakon PCI-ja.<sup>41,42</sup> Preliminarna validacija ovih rješenja pokazala je obećavajuće rezultate, međutim, potrebna je daljnja procjena tih metoda na velikome broju bolesnika prije nego se navedene metode mogu početi primjenjivati u svakodnevnoj kliničkoj praksi.

### Intravaskularno oslikavanje

Kumulativni su dokazi istaknuli vrijednost IVUS-a u provođenju PCI-ja. Metaanaliza randomiziranih kontroliranih istraživanja koja je objavljena ove godine i uključuje 4724 bolesnika naglasila je korist od IVUS-a te pokazala nižu učestalost MACE-a (5,4 % nasuprot 9,0 %,  $P < 0,001$ ), kardijalne smrti (0,6 % nasuprot 1,2 %,  $P = 0,03$ ), TLR-a (3,1 % nasuprot 5,2 %,  $P = 0,001$ ) i definitivnih, odnosno vjerojatnih tromboza stenta (0,5 % nasuprot 1,1 %,  $P = 0,02$ ) u skupini u kojoj je intervencija bila vođena IVUS-om u usporedbi s klasičnom koronarografijom.<sup>43</sup> U skladu s ovim rezultatima analiza nakon pet godina praćenja u sklopu istraživanja *Impact Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions* (IVUS-XPL) koja je uključivala 1400 bolesnika s dugim lezijama ( $\geq 28$  mm) randomiziranih na IVUS i angiografski vođenu PCI pokazala je nižu incidenciju MACE-a (5,6 % nasuprot 10,7 %,  $P = 0,001$ ) u IVUS skupini koje je pripisano nižoj incidenciji TLR-a (4,8 % nasuprot 8,4 %,  $P = 0,007$ ). Važna analiza za razdoblje praćenja od 1 do 5 godina pokazala je da je IVUS-om vođena PCI povezana s boljim kliničkim ishodima nakon dugoročnog praćenja (HR 0,53; 95 % CI 0,29 – 0,95;  $P = 0,031$ ).<sup>44</sup> Ovi rezultati pokazuju povoljan utjecaj IVUS-om vođenih revaskularizacija na prognozu i podupiru njegovu rutinsku uporabu kako bi se optimirali rezultati te poboljšali kratkoročni i dugoročni ishodi nakon PCI-ja.

FFR se trenutačno preporučuje za vođenje revaskularizacije u bolesnika s kroničnim koronarnim sindromom i srednje teškim lezijama. Istraživanje FORZA analiziralo je vrijednost OCT-a u odgađanju PCI-ja. U istraživanje je bilo uključeno 350 bolesnika sa srednje teškim lezijama koji su randomizirani na OCT i na FFR-om vođenu PCI.<sup>45</sup> Revaskularizacija u OCT skupini provedena je na temelju površine stenoze i minimalne površine lumena kao graničnih vrijednosti, dok je u FFR skupini PCI rađen ako je FFR bio  $\leq 0,80$ . OCT i FFR ponavljani su u objema skupinama te primjenjivani za optimizaciju stentova. Nakon 13 mjeseci praćenja OCT-om vođena PCI povezana je s većom incidencijom revaskularizacija te povećanim troškovima liječenja, međutim, nije bilo razlike u učestalosti MACE-a (koji je bio definiran kao kombinirani ishod ukupne

dence of non-fatal MI was higher in the iwFR group (4.7% vs. 1.9%;  $P = 0.05$ ) with a significant interaction for the presence of diabetes ( $P = 0.04$ ).<sup>40</sup>

In parallel with the introduction of the resting indices for the assessment of the functional severity of intermediate lesions, efforts have been made to design computerized-based methodologies that are able to post-process coronary angiography or invasive imaging data to derive FFR. In 2019, two new solutions have been presented for computational-derived FFR: the first relies on three-dimensional quantitative coronary angiography to derive vessel geometry and estimate the pressure drop across a lesion, while the second on the processing of OCT imaging data; the latter enables combined morphological and physiological assessment of atherosclerotic lesions and of the procedural results post-PCI.<sup>41,42</sup> Preliminary validation of these solutions showed promising results; however, further evaluation of their efficacy in a large number of patients is required before their broad application in the clinical arena.

### Intravascular imaging

Cumulative evidence has highlighted the value of IVUS in guiding PCI. A meta-analysis of randomized controlled trials published this year including 4724 patients underscored the prognostic benefit of IVUS guidance, demonstrating a lower incidence in MACE (5.4% vs. 9.0%;  $P < 0.001$ ), cardiac death (0.6% vs. 1.2%,  $P = 0.03$ ), TLR (3.1% vs. 5.2%,  $P = 0.001$ ), and definite/probable stent thrombosis (0.5% vs. 1.1%,  $P = 0.02$ ) rates in the IVUS-guided compared to the angiography-guided group.<sup>43</sup> In line with the above findings, the 5-year follow-up analysis of the Impact of Intravascular Ultrasound Guidance on Outcomes of XIENCE PRIME Stents in Long Lesions (IVUS-XPL) study that included 1400 patients with long lesions  $\geq 28$  mm randomized to IVUS- and angiography-guided PCI, reported a lower incidence of MACE (5.6% vs. 10.7%,  $P = 0.001$ ) in the IVUS-guided group attributed to a lower incidence of TLR (4.8% vs. 8.4%,  $P = 0.007$ ). A landmark analysis for the follow-up period 1–5 years indicated that IVUS guidance was associated with clinical benefit at long-term follow-up (HR 0.53, 95% CI 0.29–0.95;  $P = 0.031$ ).<sup>44</sup> These findings highlight the prognostic implications of IVUS in guiding revascularization and support its routine use to optimize procedural results and improve the short- and long-term outcomes post-PCI.

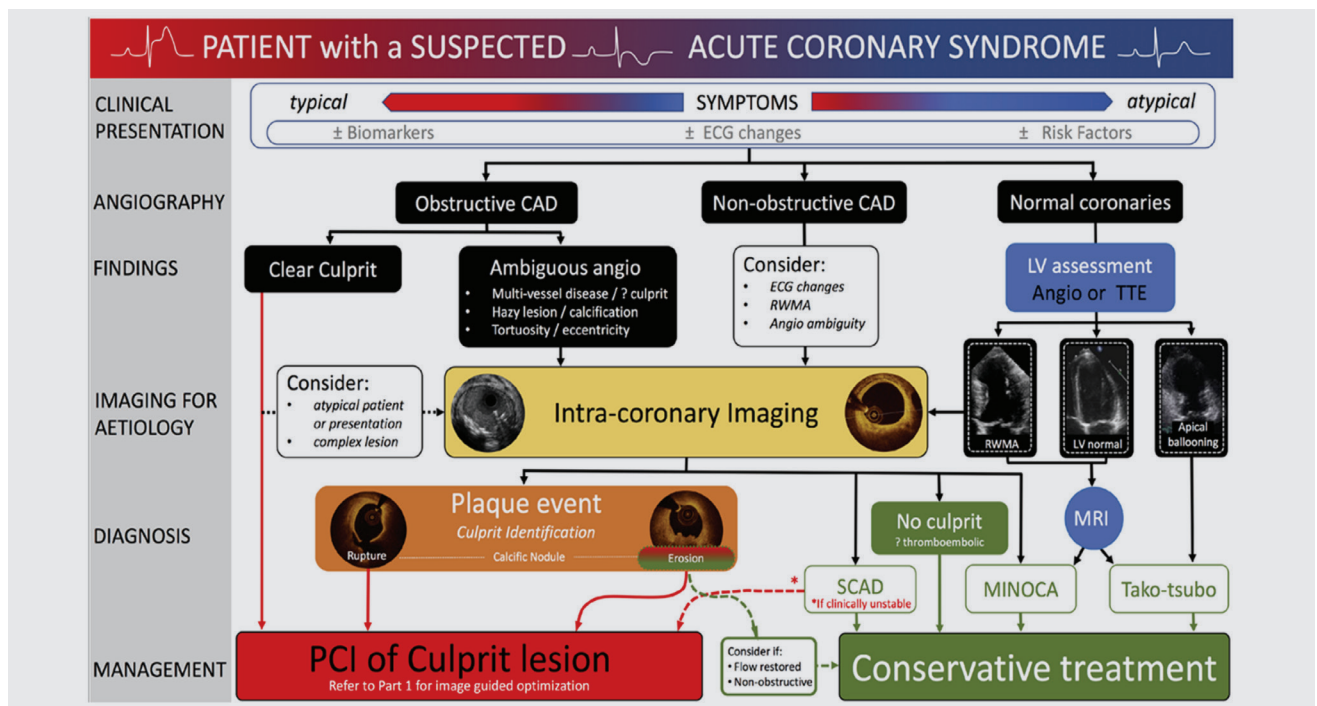
Fractional flow reserve is currently recommended to guide revascularization in patients with a chronic coronary syndrome and intermediate lesions. The FORZA study examined the value of OCT in deferring PCI; the study included 350 patients with intermediate lesions who were randomized to OCT- and FFR-guided PCI.<sup>45</sup> Revascularization in the OCT group was performed based on area stenosis and minimum lumen area cut-off values, while in the FFR group PCI was performed if the FFR was  $\leq 0.80$ . OCT and FFR were repeated in the two groups and used to optimize stent deployment. At 13 months of follow-up, OCT-guided PCI was associated with a higher incidence of revascularization and increased cost while there was no difference in the incidence of MACE—defined as the composite endpoint of all-cause death, MI, target vessel revascularization—between the FFR- and OCT-guided groups (8.0% vs. 3.4%,  $P = 0.064$ ). For the primary endpoint of the study, i.e. the incidence of MACE and significant angina at 13 months of follow-up, OCT-guided PCI was marginally superior to FFR-guidance (14.8% vs. 8.0%,  $P = 0.048$ ). The FROZA study is the first that compared in a randomized

smrtnosti, MI, revaskularizacije ciljane lezije) između FFR-om i OCT-om vođenih skupina (8,0 % nasuprot 3,4 %,  $P = 0,064$ ). Za primarni ishod istraživanja, tj. učestalost MACE-a i značajne angine nakon 13 mjeseci praćenja, OCT-om vođena PCI bila je granično superiorna FFR-om vođenoj PCI (14,8 % nasuprot 8,0 %,  $P = 0,048$ ). Studija FORZA bila je prvo istraživanje koje je uspoređivalo intravaskularnim oslikavanjem vođenu PCI s fiziološki vođenom PCI u obliku randomizirane studije te je otkrila ograničenja u obama pristupima u vođenju revaskularizacije, tj. povećane troškove procedure i broj tretiranih žila u OCT skupini i veću incidenciju MACE-a i simptoma angine u FFR-om vođenoj skupini. Pristup koji kombinira fiziološku procjenu i oslikavanje kao metode za vođenje revaskularizacije može vjerojatno zaobići ograničenja obaju modaliteta i optimirati postproceduralne rezultate i kliničke ishode u bolesnika s opstruktivnom CAD.

U 2019. Europsko udruženje za perkutane kardiovaskularne intervencije objavilo je dokument koji je rezultat suglasnosti stručnjaka o vrijednosti intravaskularnog oslikavanja u vođenju liječenja u ACS-u i dvosmislenim nalazima koronarografije.<sup>46</sup> Ovaj dokument naglašava vrijednost intravaskularnog oslikavanja ponajviše OCT-a u identifikaciji ciljane lezije kada ona ne može biti identificirana koronarografijom te u krojnoj terapiji u bolesnika primljenih zbog ACS-a (slika 3). Osim navedenog, također naglašava vrijednost intravaskularnog

fashion intravascular imaging vs. physiology guided PCI revealing limitations of both approaches in guiding revascularization (i.e. increased procedural cost and number of vessels treated in the OCT-guided group and a higher incidence of MACE and angina symptoms in the FFR-guided group). Combined physiology and imaging-guided revascularization is likely to overcome the limitations of both modalities and optimize procedural results and the clinical outcomes of patients with obstructive CAD.

In 2019, the European Association of Percutaneous Cardiovascular Interventions published an expert consensus document about the value of intravascular imaging in guiding treatment in ACS and in ambiguous coronary angiography findings.<sup>46</sup> This report highlights the value of intravascular imaging and in particular of OCT in identifying the culprit lesion when this cannot be detected by coronary angiography and in tailoring therapy in patients admitted with an ACS (Figure 3). It also underscores the value of intravascular imaging in assessing ambiguous coronary angiographic findings, in detecting embolic events and intramural haematomas, in assessing lesions caused by an external compression of the vessel by other organs and it summarizes the evidence that supports its role in identifying vulnerable plaques and high-risk patients (Figure 4).



**FIGURE 3.** Value of intravascular imaging in guiding treatment in patients admitted with an acute coronary syndrome. Intravascular imaging (intravascular ultrasound or optical coherence tomography) can be considered in patients with obstructive coronary artery disease in case of a low-risk profile, atypical presentation or complex lesion morphology. In case of multivessel disease, hazy lesions or tortuosity/eccentricity intravascular imaging can be used to identify the culprit lesion while in the absence of obstructive coronary artery disease or in the presence of normal coronary angiogram when there are regional wall motion abnormalities and electrocardiographic changes invasive imaging can be used to exclude a plaque event. Optical coherence tomography can be used to differentiate plaque rupture, plaque erosion identify an erupted calcific nodule, spontaneous coronary dissection, or thromboembolic event; in the absence of a culprit lesion magnetic resonance imaging can be considered to identify other causes such Takotsubo cardiomyopathy or myocardial infarction with non-obstructive coronary arteries. Figure was obtained with permission from Johnson et al.<sup>46</sup> This content is not covered by the terms of the CC BY-NC 4.0 Open Access agreement. Please refer to the original rightsholder.

oslikavanja u procjeni dvosmislenih nalaza koronarografije, u otkrivanju embolijskih događaja i intramuralnih hematoma, u procjeni lezija uzrokovanih vanjskom kompresijom žila od drugih organa te sumira dokaze koji podupiru ulogu OCT-a u identifikaciji ranjivih plakova i visokorizičnih bolesnika (slika 4).









### Neinvazivno oslikavanje

Neinvazivno funkcijsko oslikavanje ima uhodanu ulogu u dijagnostici opstruktivne CAD u simptomatskih bolesnika.<sup>47</sup> U istraživanju *Myocardial Perfusion CMR vs. Angiography and FFR to Guide the Management of Patients with Stable Coronary Artery Disease* (MR-INFORM) neinvazivno oslikavanje, a posebno oslikavanje magnetnom rezonancijom srca (CMR) pokazalo se korisno ne samo u dijagnostici CAD-a već i u vođenju revaskularizacije.<sup>48</sup> U tom istraživanju 918 bolesnika bilo je randomizirano na CMR-om ili FFR-om vođenu revaskularizaciju. CMR-om vođena PCI povezana je s nižom učestalosti koronarografije i PCI-ja (35,7 % nasuprot 45,0 %,  $P = 0,005$ ). Nakon jedne godine praćenja nije bilo razlike među skupinama u primarnom ishodu smrtnosti od svih uzroka, MI-ja ili revaskularizacije ciljane lezije (3,6 % nasuprot 3,7 %,  $P = 0,91$ ). Spomenuto je istraživanje jedno od rijetkih koje je uspoređivalo neinvazivno oslikavanje s invazivnim tehnikama u vođenju PCI-ja. Ograničenje tog istraživanja jest činjenica da je učestalost neželjenih događaja bila niža od 10 %, a s obzi-

### Non-invasive imaging

Non-invasive functional imaging has an established role in the diagnosis of obstructive CAD in symptomatic patients.<sup>47</sup> In the *Myocardial Perfusion CMR vs. Angiography and FFR to Guide the Management of Patients with Stable Coronary Artery Disease* (MR-INFORM) study, non-invasive imaging and in particular cardiac magnetic resonance (CMR) imaging was found to be not only useful for the diagnosis of CAD but also for guiding revascularization.<sup>48</sup> In this study, 918 patients were randomized to CMR- or FFR-guided revascularization. CMR-guided PCI was associated with a lower incidence of coronary angiography and PCI (35.7% vs. 45.0%,  $P = 0.005$ ). At 1-year follow-up, there was no difference between groups for the primary endpoint of all-cause mortality, MI, or target vessel revascularization (3.6% vs. 3.7%,  $P = 0.91$ ). This report is among the few that compared the role of non-invasive imaging vs. invasive guidance for PCI. A limitation of this study is the fact that the event rate was lower than the 10% event rate assumed in the power calculation and thus it may have been underpowered in detecting differences in outcomes between the two study groups.

Similar were the findings of the *Complete Revascularization or Stress Echocardiography in Patients With Multivessel Disease and ST-Segment Elevation Acute Myocardial Infarc-*

	Study	Modality	Number of patients	Follow-up period	Clinical endpoint	Imaging predictors	Hazard ratio (95% CI)	PPV	NPV
Lesion level analysis	PROSPECT		697	3.4 years	Cardiac death or arrest, MI or rehospitalisation due to unstable or progressive angina	PB $\geq$ 70% MLA $\leq$ 4mm <sup>2</sup> TCFA	5.03 (2.51–10.11) 3.21 (1.61–6.42) 3.35 (1.77–6.36)	18.2%	98.1%
	VIVA		170	1.7 years	Death, MI, unplanned revascularisation	PB>70% TCFA RI	8.13(1.63-40.56) 7.53(1.12-50.55) 2.69 (1.94- 3.72)	-	-
	PREDICTION		506	1 year	PCI because of clinical events or disease progression on angiography	PB $\geq$ 58% ESS<1Pa	17.57 (3.67-84.20) 3.18 (1.20-8.43)	41%	92%
	LRP		1563	2 years	Cardiac death or arrest, ACS, revascularisation, readmission for angina and >20% DS progression on angiography	maxLCBI <sub>4mm</sub> $\geq$ 400	3.39 (1.85–6.20)	-	-
	CLIMA		1003	1 year	Cardiac death, target vessel myocardial infarction	MLA <3.5 mm <sup>2</sup> FCT <75 $\mu$ m lipid arc >180° macrophages	2.07 (1.10-4.00) 4.65 (2.40-9.00) 2.40 (1.20-4.80) 2.66 (1.20-6.10)	18.9%	97.0%
Patient level analysis	Atheroremo (IVUS)		581	1 year	All cause death, ACS, or unplanned coronary revascularization	PB>70% TCFA	2.83 (1.57– 5.13) 1.97 (1.09– 3.57)	20.5%	93.9%
	Atheroremo (NIRS)		203	1 year	All cause death, ACS, stroke and unplanned coronary revascularization exclusive of events related to the culprit lesion	LCBI $\geq$ 43	5.16 (1.73–15.42)	-	-
	LRP		1563	2 years	Cardiac death or arrest, ACS, revascularisation, readmission for angina and >20% DS progression on angiography	maxLCBI <sub>4mm</sub> $\geq$ 400	1.89 (1.26–2.83)	-	-

**FIGURE 4. Summary of the studies investigating the efficacy of intravascular imaging in detecting high-risk plaques and patients. The studies' endpoints, the imaging predictors and the hazard ratio and the confidence interval of the imaging biomarkers are summarized, while the positive and negative predictive values are shown only for large scale studies with more than one imaging biomarkers as independent predictor.**

ACS, acute coronary syndrome; CI, confidence interval; DS, diameter stenosis; ESS, endothelial shear stress; FCT, fibrous cap thickness; LCBI, lipid core burden index; MI, myocardial infarction; MLA, minimum lumen area; NPV, negative predictive value; PB, plaque burden; PCI, percutaneous coronary intervention; PPV, positive predictive value; RI, remodelling index; TCFA, thin cap fibroatheroma.

rom na to da je 10 % neželjenih događaja uzeto pri računanju snage, istraživanje je potencijalno bilo preslabe snage da bi detektiralo razlike u ishodima između skupina.

Slični su rezultati nađeni u istraživanju *Complete Revascularization or Stress Echocardiography in Patients With Multivessel Disease and ST-Segment Elevation Myocardial Infarction* (CROSS-AMI) koje je uspoređivalo angiografijom i stresnom ehokardiografijom vođenu revaskularizaciju u bolesnika primljenih sa STEMI-jem koji su imali leziju koja nije bila uzrok infarkta sa stenozom dijametra >50 % na kvantitativnoj koronarografiji.<sup>49</sup> Istraživanje je prerano zaustavljeno nakon uključivanja 77 % predviđenih bolesnika zbog sporog uključivanja bolesnika (n = 306). Autori su prijavili veću incidenciju revaskularizacije lezija koje nisu uzorkovale infarkt u angiografskoj skupini (80 % nasuprot 22 %). Nakon jedne godine praćenja nije bilo razlike između skupina u primarnom ishodu od kardiovaskularne smrtnosti, MI, koronarne revaskularizacije ili rehospitalizacije zbog zatajivanja srca (14 % nasuprot 14 %, P = 0,85). Ograničenje CROSS-AMI studije leži u činjenici da nije bila dovoljno snažna kako bi procijenila razlike između skupina. S obzirom na navedeno, potrebna su daljnja istraživanja kako bi se utvrdila vrijednost neinvazivnog oslikavanja u vođenju revaskularizacije u bolesnika s ACS-om.

## Ranjivi plakovi i identifikacija bolesnika

Učestalost neželjenih događaja u bolesnika podvrgnutih revaskularizaciji, a poglavito u onih primljenih s ACS-om visoka je nakon kratkoročnog praćenja.<sup>50</sup> Identifikacija visokorizičnih bolesnika nedavno je privukla pozornost s obzirom na to da su uvedene nove farmakoterapijske metode koje potencijalno mogu modificirati aterosklerotski plak i inhibirati progresiju bolesti. Međutim, ove, nove terapije imaju znatna ograničenja jer su povezane s povećanim troškovima ili nuspojavama. Očekuje se da bi precizna stratifikacija rizika i identifikacija bolesnika pod visokim rizikom mogla dovesti do personalizirane terapije i agresivnog liječenja ovakvih bolesnika novim lijekovima čiji bi učinak mogao poboljšati ishode u osjetljivim populacijama.<sup>51</sup>

Velika prospektivna istraživanja intravaskularnog oslikavanja koronarne ateroskleroze naglasila su vrijednost IVUS-a u detekciji ranjivih plakova koji bi mogli progredirati te uzrokovati neželjene događaje te u boljoj stratifikaciji kardiovaskularnog rizika. Tijekom 2019. godine istraživanja *Lipid-Rich Plaque* (LRP) i CLIMA prvi su put procjenjivala efikasnost spektroskopije blizu infracrvenoga spektra (NIRS)-IVUS-a i OCT-a u detekciji ranjivih plakova.<sup>52,53</sup> Registar LRP uključio je 1563 bolesnika sa sumnjom na CAD koji su imali nalaz koronarografije i potencijalni *ad hoc* PCI. NIRS-IVUS oslikavanje rađeno je na lezijama koje nisu uzrok MI-ja u barem dvjema velikim koronarnim arterijama s duljinom >50 mm. Nakon 2 godine praćenja bolesnici s povećanim teretom lipida (4 mm indeks tereta jezgre lipida,  $\text{maxLCBI}_{4\text{mm}} > 400$ ) imali su veću incidenciju non-culprit MACE-a nego oni s plakovima bez lipida (13 % nasuprot 6 %, P < 0,0001). Analize na razini bolesnika (prilagođeni HR 1,89; 95 % CI 1,26 – 2,83, P = 0,0021) i na razini lezije (prilagođeni HR 3,39; 95 % CI 1,85 – 6,20, P < 0,001) pokazale su da je  $\text{maxLCBI}_{4\text{mm}} > 400$  neovisni prediktor MACE-a nakon 2 godine praćenja. Istraživanje LRP pružilo je dokaze utjecaja sastava plaka na ishode, ali nije istražila sinergistički učinak NIRS-a i IVUS-a u predviđanju neželjenih događaja jer

tion (CROSS-AMI) study that compared angiography vs. stress echocardiography-guided revascularization in patients admitted with a STEMI that had non-culprit lesions with a diameter stenosis >50% on quantitative coronary angiography.<sup>49</sup> The study was prematurely stopped after enrolling 77% of the patients because of a slow recruitment (n = 306). The authors reported a higher incidence of non-culprit lesion revascularization in the angiography group (88% vs. 22%). At 1-year follow-up, there were no differences between groups for the primary endpoint of cardiac death, MI, coronary revascularization, or re-admission because of heart failure (14% vs. 14%, P = 0.85). A limitation of the CROSS-AMI study was the fact that it was underpowered to assess differences between groups. Therefore, further research is needed to examine the value of non-invasive imaging in guiding revascularization in patients with an ACS.

## Vulnerable plaque and patient detection

The event rate of patients undergoing revascularization and especially of those admitted with an ACS is high- at short-term follow-up.<sup>50</sup> The identification of high-risk patients has recently attracted attention as novel pharmacotherapies have been introduced that appear able to modify atherosclerotic plaque and inhibit disease progression. However, these new therapies have significant limitations as they are associated with increased cost or side effects. Accurate risk stratification and identification of high-risk individuals is expected to allow a personalized therapy and aggressive treatment of these patients with novel medications that appear to improve outcomes in vulnerable populations.<sup>51</sup>

Large scale prospective intravascular imaging studies of coronary atherosclerosis have highlighted the value of IVUS in detecting vulnerable plaques that are likely to progress and cause events and in stratifying more accurately cardiovascular risk. In 2019, the Lipid-Rich Plaque (LRP) and the CLIMA studies were reported which for the first time assessed the efficacy of near-infrared spectroscopy (NIRS)-IVUS and of OCT in detecting vulnerable plaques.<sup>52,53</sup> The LRP registry included 1563 patients with suspected CAD that had coronary angiography and possible *ad hoc* PCI. NIRS-IVUS imaging was performed in the non-culprit vessels in at least two major coronary arteries with length >50 mm. At 2-year follow-up, patients with increased lipid burden (4 mm lipid core burden index,  $\text{maxLCBI}_{4\text{mm}} > 400$ ) had a higher incidence of non-culprit MACE than those with lipid-free plaques (13% vs. 6%, P < 0.0001). Patient-level (adjusted HR 1.89, 95% CI 1.26–2.83; P = 0.0021) and lesion-level (adjusted HR 3.39, 95% CI 1.85–6.20; P < 0.0001) analysis demonstrated that  $\text{maxLCBI}_{4\text{mm}} > 400$  was independent predictor of MACE at 2-year follow-up. The LRP study provided evidence for the prognostic implications of plaque composition but it failed to investigate the synergetic value of NIRS and IVUS in predicting events as IVUS analysis was not complete but restricted to the 4 mm segment with the  $\text{maxLCBI}$ .

The CLIMA study was a prospective multicentre registry that investigated the prognostic implications of OCT-derived plaque characteristic in 1003 patients who had coronary angiography for clinical purposes and OCT imaging of the untreated proximal left anterior descending coronary artery.<sup>53</sup> In this study, a minimum lumen area <3.5 mm<sup>2</sup>, a lipid arc >180°, a fibrous cap thickness <75 μm, and the presence of macrophages accumulations were independent predictors of the combined

analiza IVUS-a nije potpuna, nego je ograničena na segment od 4 mm s maxLCBI.

Istraživanje CLIMA bilo je prospektivni multicentrični registar koji je istraživao utjecaj OCT-om izračunanih obilježja plaka u 1003 bolesnika s koronarografijom zbog kliničkih razloga i OCT oslikavanjem neliječenih lezija proksimalne LAD na prognozu bolesnika.<sup>53</sup> U tom istraživanju minimalna površina lumena <3,5 mm<sup>2</sup>, luk lipida >180 stupnjeva, fibrozna kapa debljine <75 μm i prisutnost nakupina makrofaga bili su neovisni prediktori kombiniranog ishoda kardiovaskularne smrtnosti i MI ciljnog segmenta. Bolesnici s lezijama koje su imala sva navedena obilježja imali su veću stopu neželjenih događaja u usporedbi s drugim bolesnicima (18,9 % nasuprot 3,0 %, P <0,001).

## Napredak u koronarnom oslikavanju

Sumirajući rezultate spomenutih istraživanja i uzimajući u obzir rezultate prijašnjih istraživanja, čini se da obilježja plaka daju korisne prognostičke informacije na razini lezije i bolesnika, ali imaju ograničenu točnost u predviđanju događaja. Tijekom prošle godine uvedeno je nekoliko metodologija kako bi se unaprijedila učinkovitost postojećih modaliteta u procjeni obilježja plakova te je uloženi trud u razvoj hibridnog multimodalnog intravaskularnog katetera koji će omogućiti potpunu procjenu morfologije i biologije plakova. Tijekom 2019. prvi put je u ljudi primijenjen kombinirani IVUS-OCT kateter.<sup>54</sup> Usto, prvi je put u ljudi primijenjen i na polarizaciju osjetljivi OCT sustav oslikavanja. Očekuje se da bi ovaj modalitet mogao omogućiti detaljniju procjenu plakova i njegovih sastavnica.<sup>55</sup> Konačno, dva su istraživanja nedavno istražila učinkovitost atenuacijsko-kompenzacijske tehnike. To je metoda naknadne obrade koja bi potencijalno mogla poboljšati dubinu oslikavanja OCT-om i pružiti točniju procjenu težine plaka u izrazito bolesnim segmentima.<sup>56,57</sup> Spomenuta su istraživanja naglasila potencijal ovakvog pristupa u procjeni površine plakova u izrazito bolesnim nativnim žilama, ali su također pokazala znatna ograničenja navedene tehnike zbog artefakata na slikama u segmentima sa stentovima.

Kumulativni su dokazi naglasili upletenost lokalnih hemodinamskih sila na progresiju i destabilizaciju aterosklerotske bolesti. U 2019. analiza studije *Integrated Biomarkers Imaging Study 4* (IBIS-4) pokazala je da distribucija smičnoga stresa koja je procijenjena primjenom računalne analize dinamike fluida daje dodatnu vrijednost u predviđanju progresije aterosklerotske bolesti i promjena u morfologiji plaka. Metaanaliza istraživanja *Providing Regional Observations to Study Predictors of Events in the Coronary Tree* (PROSPECT) pokazala je da procjena stresa plaka kroz procesiranje slika dobivenih IVUS-om kroz virtualnu histologiju omogućuje identifikaciju lezija koje će uzrokovati događaje u budućnosti.<sup>58,59</sup> Priznajući važnost lokalnih hemodinamskih sila na progresiju aterosklerotske bolesti u nativnim i stentiranim segmentima, nedavno su objavljene stručne preporuke u zajedničkom dokumentu koji opisuje postojeću metodologiju i njezinu vrijednost u istraživanju i potencijalno u kliničkoj praksi u budućnosti.<sup>60</sup>

## Zaključak

Istraživanja koja su objavljena tijekom 2019., a istraživala su utjecaj različitih strategija liječenja, novih i postojećih uređaja te vrijednosti koronarne fiziologije i oslikavanja u planira-

endpoint cardiac death and target segment MI. Patients having lesions with all the above plaque features had a higher event rate than the other patients (18.9% vs. 3.0%, P < 0.001).

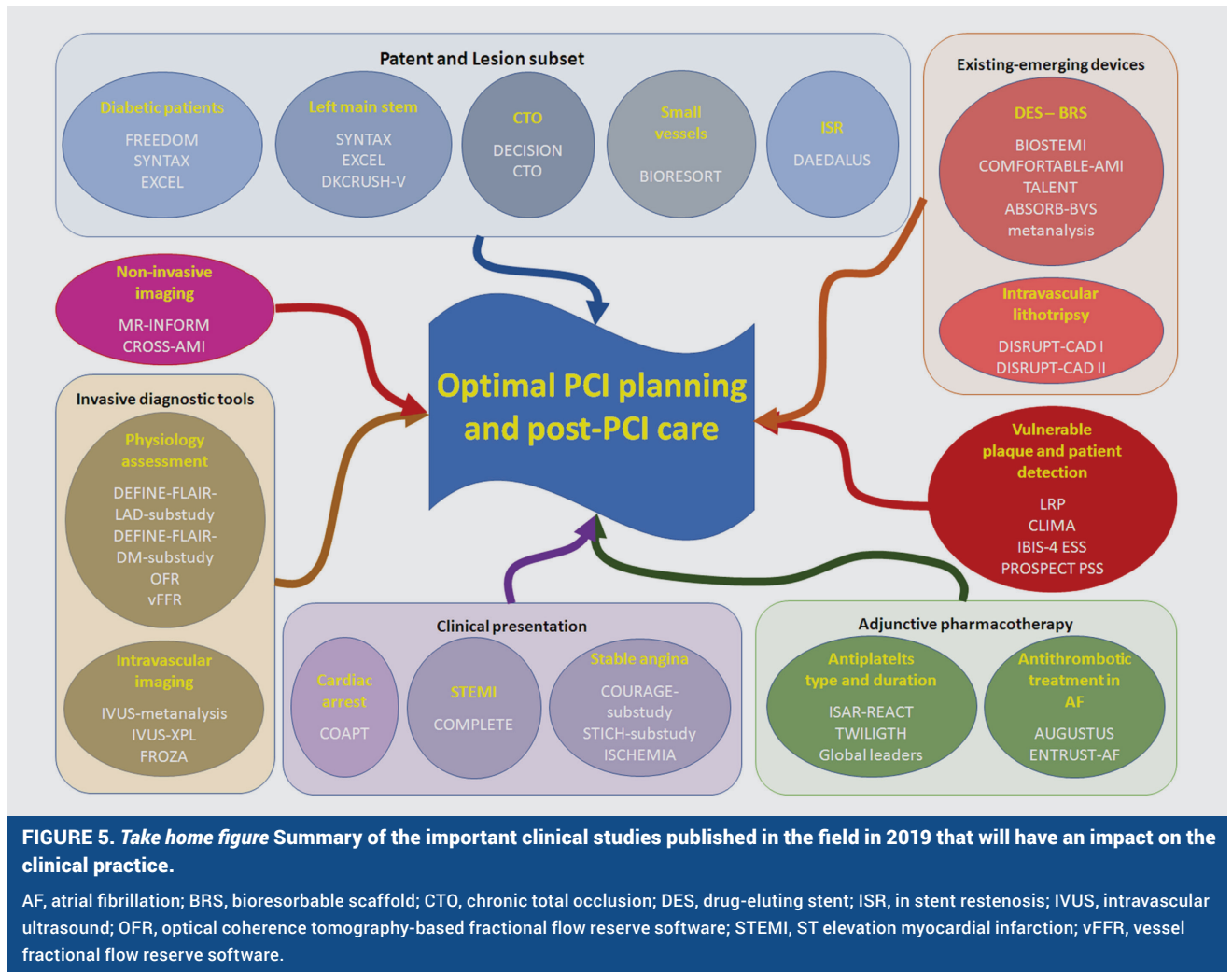
## Advances in coronary imaging

Summarizing the results of these studies and taking into consideration the findings of previous reports it appears that plaque characteristics provides useful prognostic information at a lesion and patient level; but they have a limited accuracy in predicting events. Over the last years, several methodologies have been introduced to enhance the efficacy of the existing modalities in assessing plaque characteristics and an effort has been made to develop hybrid-multimodality intravascular imaging catheters that will allow a complete assessment of plaque morphology and biology. In 2019, the first in man application of the combined IVUS-OCT catheter has been presented.<sup>54</sup> In addition, this year the first in man application of a polarization sensitive OCT imaging system was presented; this modality is expected to enable better plaque characterization and more detailed evaluation of its components.<sup>55</sup> Finally, two reports have recently examined the efficacy of attenuation compensation technique, a post-processing methodology that appears able to enhance OCT imaging depth and enable more accurate evaluation of plaque burden in heavily diseased segments.<sup>56,57</sup> These reports highlighted the potential of this approach in assessing plaque area in heavily diseased native vessels but also demonstrated significant limitations of this technique, because of imaging artefacts, in stented segments.

Cumulative evidence has highlighted the implications of the local haemodynamic forces on atherosclerotic disease progression and destabilization. In 2019, an analysis of the *Integrated Biomarkers Imaging Study 4* (IBIS-4) has shown that the shear stress distribution estimated using computational fluid dynamic analysis adds value in predicting atherosclerotic disease progression and changes in plaque morphology, while a meta-analysis of the *Providing Regional Observations to Study Predictors of Events in the Coronary Tree* (PROSPECT) study has shown that estimation of plaque stress by processing virtual histology-IVUS images enables more accurate identification of lesions that will cause events in future.<sup>58,59</sup> Acknowledging the importance of the local haemodynamic forces on atherosclerotic disease progression in native and stented segments expert recommendations have been recently published in a consensus document which describes the existing methodologies and their value for research and possibly clinical practice in the future.<sup>60</sup>

## Conclusions

Published research in 2019 examining the efficacy of different treatment strategies, of emerging or existing devices and of the value of coronary physiology or intravascular imaging in PCI planning has enriched our understanding and modified the treatment of patients with obstructive CAD (**Figure 5**). Patients suffering from a STEMI should be treated aggressively aiming for complete revascularization. Conversely, an initially conservative management in patients with an out of hospital cardiac arrest without clinical evidence of ongo-



nju PCI-ja obogatila su naše razumijevanje i modificirala liječenje bolesnika s opstruktivnom CAD (slika 5). Bolesnici sa STEMI-jem trebali bi biti agresivno liječeni ciljajući na potpunu revaskularizaciju. Suprotno tomu, inicijalno konzervativni pristup u zbrinjavanju bolesnika s izvanbolničkim arestom bez kliničkih dokaza ishemije čini se jednako učinkovit kao rani invazivni pristup. Opsežna količina dokaza naglašava kratkoročnu i dugoročnu učinkovitost DES-a, dok napredak u koronarnoj fiziologiji i razvoj metodologija temeljenih na oslikavanju za izračun FFR-a očekuje proširiti njegovu primjenu u vođenju revaskularizacije. Sveukupni podatci ističu prognostičku korisnost od intravaskularnog oslikavanja u vođenju PCI-ja i procjeni patologije lezija, dok se za napredak u intravaskularnom oslikavanju i računalnom modeliranju očekuje da bi mogli dovesti do boljeg predviđanja ranjivih lezija i bolesnika pod rizikom koji će imati koristi od izranjajućih terapija koje ciljaju razvoj plakova. Očekuje se da bi navedeni napredci mogli unaprijediti postproceduralne rezultate i dugoročne ishode u bolesnika s CAD-om kroz personalizirane farmako-invazivne strategije.

ing acute ischaemia seems to be equally effective as an early invasive approach. Robust evidence highlights the short- and long-term efficacy of DES, while advances in coronary physiology and the development of image-based methodologies for the computation of FFR are expected to broaden its use in guiding revascularization. Cumulative data underscore the prognostic benefit of intravascular imaging in guiding PCI and in assessing lesion pathology, while advances in intravascular imaging and computational modelling are anticipated to allow better prediction of vulnerable lesions and of patients at risk that will benefit from emerging therapies targeting plaque evolution. These developments are expected to improve procedural results and long-term outcomes in patients with CAD through personalized pharmaco-invasive strategies.

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