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

REVASCULARISATION IN PATIENTS WITH CARDIAC ARREST OR ACUTE CORONARY SYNDROMES

Coronary Angiography after Cardiac Arrest (COACT) is a landmark study that changed the management of patients admitted with a cardiac arrest who had successful resuscitation and no ST elevation myocardial infarction (STEMI). 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 randomised to immediate coronary angiography and if needed coronary revascularisation or delayed coronary angiography after neurological recovery. An acute thrombotic occlusion was noted only in 3.4% of patients in the immediate angiography and in 7.6% of patients 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 randomisation 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 penalised a delayed invasive assessment of the coronary artery anatomy and justify both approaches in this setting.

Conversely, the Complete vs. Culprit-Only Revascularisation Strategies to Treat Multivessel Disease after Early PCI for STEMI (COMPLETE) study confirmed the value of an aggressive revascularisation strategy in patients admitted with a STEMI. In this study, 4 041 patients who had multivessel CAD were randomised in a 1:1 ratio to complete revascularisation 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 revascularisation 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 revascularisation 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 randomised, as the choice for timing of the second procedure was left to operator’s discretion. The prognostic value of complete revascularisation in patients with non-STEMI has not been fully investigated yet.

INTRODUCTION

Percutaneous coronary intervention (PCI) research focuses on the optimisation 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 summarise the findings of the pivotal studies published in 2019 and to discuss their impact on clinical practice.
CHRONIC CORONARY SYNDROMES

Revascularisation vs. medical therapy

Despite the robust evidence supporting the prognostic implications of complete revascularisation 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 postinmission computed tomography myocardial perfusion imaging, demonstrated that an early surgical or percutaneous revascularisation was associated with improved prognosis in patients with an ischaemic burden >5% - 10%.(3) These findings, however, were not confirmed in a post hoc analysis of the Clinical Outcomes Utilising Revascularisation and Aggressive Drug Evaluation (COURAGE) trial that included 1,379 patients who had stress perfusion imaging and quantitative coronary angiography.(4) 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 interaction between the extent of ischaemia or CAD and the treatment strategy (i.e. conservative vs. PCI).

In line with these findings, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA study) that included 5,179 patients with moderate or severe ischaemia in non-invasive imaging, who were randomised 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).(5) 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 revascularisation, and clinical outcomes was recently evaluated by a post hoc analysis of the Surgical Treatment for Ischaemic Heart Failure (STICH) study.(6) This analysis, which included 601 patients who had a left ventricular ejection fraction ≤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 revascularisation at 10.4-year follow-up. The REvascularisation 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 revascularisation strategy in patients with advanced CAD [i.e. 3-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 revascularisation: surgical revascularisation is currently the recommended treatment strategy in diabetic patients with multivessel CAD, while PCI has a IIB indication in patients with a SYNTAX score ≤22 and is not recommended in patients with a SYNTAX score >22.(7)

These recommendations are in line with the findings of the Future Revascularisation Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) Follow-On study, which included 1,900 diabetic patients with multivessel disease who were randomised to surgical or percutaneous revascularisation and reported a higher mortality rate at 8 years of follow-up in the PCI arm compared to the surgical revascularisation group (24.3% vs. 18.3%, p=0.01). Conversely, the Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) Extended Survival study that included 1,689 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 interaction according to the presence or absence of 3-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 were no differences between the 2 groups in patients with LMS disease (HR 0.90, 95% CI 0.68 - 1.20); conversely, there was no difference in outcomes for the 2 treatment strategies in diabetic and non-diabetic patients (P-for interaction 0.660). 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-oriented cardiovascular endpoints.

The Evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularisation (EXCEL) study overcame these limitations; in this study, 1,905 patients with
LMS disease and SYNTAX score ≤32 were randomised to PCI with a 2nd generation DES or CABG. In the PCI arm, intravascular ultrasound (IVUS) imaging was used in 77.2% of the cases. 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 - 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 randomised 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 revascularisation (16.9% vs. 10.0%). Similarly to what has been reported in the SYNTAX study, there was no difference in the outcomes between the 2 treatment strategies in diabetic and non-diabetic patients at 3- and 5-year follow-up.

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, the double kiss-crush technique was associated with a lower incidence of target lesion revascularisation (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. The 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 a provisional T-stenting technique for the treatment of bifurcation lesions and proposes a 2-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 >5mm from the carina and/or increased calcification. In the case of a 2-stent strategy, the European Bifurcation Club recommends the use of culotte or the TAP technique and when the crush technique is considered it proposes the use of the double kiss-crush.

Treatment of chronic total occlusions

In 2019, the EuroCTO Club published a consensus document that summarises the current evidence (Figure 1), discusses the indications for chronic total occlusion (CTO) revascularisation, presents the advances in CTO equipment, and provides recommendations about training in CTO PCI. In line with the ESC guidelines on myocardial revascularisation and taking into account the findings of randomised controlled studies, the EuroCTO Club recommends CTO recanalisation in the presence of symptoms despite optimal medical therapy; in asymptomatic patients, ischaemic burden assessment is recommended and CTO revascularisation is advised if there is evidence of increased ischaemic burden (>10% of the left ventricular mass). These recommendation 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. This study, 815 patients with a CTO were randomised in a 1:1 ratio to complete revascularisation or to the treatment of the obstructive non-CTO lesions whenever these were present. Only one-fourth of the patients included in the 2 groups had a single-vessel disease. At 4-year follow-up, there was no difference between the 2 groups for the combined endpoint of death, MI, stroke, or revascularisation (22.4% vs. 22.3%, p=0.86) or patients’ quality of life. These findings indicate that in case of multivessel disease, revascularisation of the non-CTO lesion and re-evaluation of the extent of ischaemia and patient symptoms should be considered before advocating recanalisation 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 randomisation, as well the fact that it was underpowered for the primary endpoint as patient recruitment was terminated early 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, which compared outcomes following PCI in small vessels (<2.5mm) using ultrathin-strut cobalt chromium biodegradable polymer sirolimus-eluting stents (strut thickness 71μm) or very thin-strut platinum chromium biodegradable polymer everolimus-eluting stents (strut thickness 78μm) or previous-generation thin strut cobalt-chromium durable polymer zotarolimus-eluting stents (strut thickness 102μm). A higher incidence of TLR was noted in the thicker strut zotarolimus-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.
**FIGURE 1:** Summary of the findings of the 3 randomised control trials comparing percutaneous coronary intervention and medical therapy in patients with a total chronic occlusion.

Reproduced with permission from ref.(15)  Percutaneous recanalisation of chronic total occlusions: 2019 consensus document from the EuroCTO Club. Page no. 198 - 208, Copyright 2019, with permission from Europa Digital & Publishing. This content is not covered by the terms of the CC BY-NC 4.0 Open Access agreement. Please refer to the original rightsholder.

| Location & design | Explore | Eurocto | Impactor-CTO |
|------------------|---------|---------|--------------|
| Location         | Europe & Canada | Europe | Russia |
| Design           | Multicentre RCT (14 centres) | Multicentre RCT (28 centres) | Single-centre RCT |

| N patients | 304 | 407 | 72 |
|------------|-----|-----|----|

| Study population | Explore | Eurocto | Impactor-CTO |
|------------------|---------|---------|--------------|
| Patients treated | Patients with STEMI treated with PCI with a non-infarct-related CTO | SCAD CTO patients with symptoms and/or ischaemia and viability | Patients with isolated dominant RCA CTO and stable angina |

| Primary endpoint | Explore | Eurocto | Impactor-CTO |
|------------------|---------|---------|--------------|
| LVEF and LVEDV by CMR | QoL (SAQ, EQ-5D) | ΔMIB by a adenosine stress CMR |

| Follow-up period | 4 months | 1 year | 1 year |
|------------------|----------|--------|--------|

| Mean J-CTO score | 2 ± 1 | 1.82 ± 1.07 | 1.92 ± 0.86 |
|------------------|-------|-------------|-------------|

| Success rate | Explore | Eurocto | Impactor-CTO |
|--------------|---------|---------|--------------|
| 73.0%        | 86.6%   | 83.0%   |

| Positive/negative | Explore | Eurocto | Impactor-CTO |
|-------------------|---------|---------|--------------|
| -                 | +       | +       |

| Major findings | PCI | OMT | PCI | OMT | PCI | OMT |
|----------------|-----|-----|-----|-----|-----|-----|
| MACE            | No difference | No difference | No difference | No difference | No difference |
| QoL             | N/A | N/A | Better | Better | N/A |
| Ischaemia reduction | N/A | N/A | Better | Better | N/A |
| LVEF and LVEDV  | PCI of a CTO located in the LAD may improve LVEF and clinical outcome | No difference | Better | Better | No difference |

CMR = cardiac magnetic resonance, CTO = chronic total occlusion, EQ-SD = EuroQol 5 dimensions questionnaire, J-CTO = Japanese chronic total occlusion, LAD = left anterior descending, LVEDV = left ventricular end-diastolic volume, LVEF = left ventricular ejection fraction, MACE = major adverse cardiovascular events, OMT = optimal medical therapy, PCI = percutaneous coronary intervention, QoL = quality of life, RCA = right coronary artery, RCT = randomised control trial, SAQ = Seattle Angina Questionnaire, SCAD = stable coronary artery disease, STEMI = ST-segment elevation myocardial infarction, ΔMIB = decrease in myocardial ischaemia burden.
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.

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. The 2 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, which included 1,976 patients treated with a paclitaxel-coated balloon or a DES. At 3-year follow-up, paclitaxel-coated balloon angioplasty was associated with a higher incidence of TLR compared 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).

**EXISTING AND EMERGING INTERVENTIONAL DEVICES**

**Drug-eluting stents and bioresorbable scaffolds**

The ESC Guidelines on myocardial revascularisation recommend the use of 2nd generation DES in daily clinical practice. 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. \(^{(21)}\)

The BIOSTEMI study also focused on the treatment of patients with STEMI and randomised 1 300 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). \(^{(22)}\) Conversely, the TALENT study that compared outcomes in all-comer patients randomised 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%, \( p \) for non-inferiority <0.0001). \(^{(23)}\)

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 they are not recommended for routine clinical use. A recent meta-analysis of randomised studies comparing the Absorb biodegradable 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. \(^{(24)}\) 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 biodegradable scaffolds and indicate a low event rate at long term after their full resorption.

Adju nctive 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. \(^{(25)}\) It involves the advancement of a catheter with a balloon on its tip that contains multiple emitters that generate sonic pressure waves that selectively fracture vascular calcium without affecting the integrity of the fibroelastic tissue of the plaque. \(^{(26)}\) The Shockwave 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 ≤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%, 3 peri-procedural MI and 2 cardiac deaths were reported. \(^{(27)}\) Similar findings were in 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 ± 2.6 fractures per lesion, resulting in an acute gain of 4.79 ± 2.45 mm\(^2\) and an excellent stent expansion of 102.8 ± 30.6%. \(^{(28)}\) Recently, Wilson, et al. \(^{(29)}\) 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. \(^{(30)}\) The study randomised 7 119 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 4 570 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 8 randomised control trials including 14 963
patients, which demonstrated that in low bleeding risk patients (PR6dicting 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.(31)

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 several large scale randomised control studies over recent years. The AUGUSTUS trial published this year was a multicentre randomised study with a 2 x 2 factorial design that randomised 4 614 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。(32)

The recruited patients received standard of care antithrombotic therapy in the first days post-PCI as randomisation 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 a 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 hospitalisation 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 on these endpoints.

Similar were the findings of the ENTRUST-AF PCI study, which investigated in 1 506 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。(33) The recruited patients were randomised to the 2 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 randomised 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。(34)

**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 revascularisation, but also in assessing the final results post-PCI and predicting prognosis。(35,36) 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 resting indices. A recent sub-analysis of the Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation (DEFINE-FLAIR) study comparing outcomes in patients with a lesion in the left anterior descending coronary artery deferred from revascularisation 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 revascularisations (2.22% vs. 4.99%, p=0.03)。(37) 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 incidence 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)。(38)

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 computerised-based methodologies that are able to post-process coronary angiography or invasive imaging data to derive FFR. In 2019, 2 new solutions have been presented for computational-derived FFR: the first relies on 3-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。(41,42) 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 randomised controlled trials published this year including 4 724 patients underscored the prognostic benefit of IVUS guidance, demonstrating a lower incidence in MACE (5.4% vs. 9.0%; P <0.001), cardiac death
Fractional flow reserve is currently recommended to guide revascularisation 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 randomised to OCT- 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). These findings highlight the prognostic implications of IVUS in guiding revascularisation and support its routine use to optimise procedural results and improve the short- and long-term outcomes post-PCI.

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. 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 summarises the evidence that supports its role in identifying vulnerable plaques and high-risk patients (Figure 4).

Non-invasive imaging

Non-invasive functional imaging has an established role in the diagnosis of obstructive CAD in symptomatic patients. 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 revascularisation. In this study, 918 patients were randomised to CMR- or FFR-guided revascularisation. 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 revascularisation (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 findings occurred with the Complete Revascularisation or Stress Echocardiography in Patients With Multivessel Disease and ST-Segment Elevation Acute Myocardial Infarction (CROSS-AMI) study that compared angiography vs. stress echocardiography-guided revascularisation in patients admitted with a STEMI that had non-culprit lesions with a diameter stenosis >50% on quantitative coronary angiography. 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 revascularisation 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 revascularisation, or
re-admission because of heart failure (14% vs. 14%, p=0.85).
A limitation of the CROSS-AMI study was that it was under-powered to assess differences between groups. Therefore, further research is needed to examine the value of non-invasive imaging in guiding revascularisation in patients with an ACS.

VULNERABLE PLAQUE AND PATIENT DETECTION

The event rate of patients undergoing revascularisation and especially of those admitted with an ACS is high at short-term follow-up. The identification of high-risk patients has recently
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 summarised, while the positive and negative predictive values are shown only for large-scale studies with more than one imaging biomarker as independent predictor.

| Study                | Modality     | Number of patients | Follow-up period | Clinical endpoint                                                                 | Imaging predictors | Hazard ratio (95% CI) | PPV   | NPV   |
|----------------------|--------------|--------------------|------------------|-----------------------------------------------------------------------------------|--------------------|-----------------------|-------|-------|
|                      |              |                    |                  |                                                                                    |                    |                       |       |       |
| Lesion levels analysis |              |                    |                  |                                                                                    |                    |                       |       |       |
| Prospect             |              | 697                | 3.4 years        | Cardiac death or arrest, MI or rehospitalisation due to unstable or progressive angina. | PB ≥70% MLA ≤4mm² TCF A | 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% TCF A 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 ≥58% ESS <1Pa | 17.57 [3.67 - 84.20] 3.18 [1.20 - 8.43] | 41%   | 92%   |
| LRP                  |              | 1,563              | 2 years          | Cardiac death or arrest, ACS, revascularisation, readmission for angina and >20% DS progression on angiography. | maxLCBI ≥400 | 3.39 [1.85 - 6.20] | -     | -     |
| CLIMA                |              | 1,003              | 1 year           | Cardiac death, target vessel myocardial infarction.                              | MLA <3.5mm² FCT <75µm 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%   |
| Athero D [IVUS]      |              | 581                | 1 year           | All cause death, ACS, or unplanned coronary revascularisation.                    | PB >70% TCF A | 2.83 [1.57 - 5.13] 1.97 [1.09 - 3.57] | 20.5% | 93.9% |
| Athero D [NIRS]      |              | 203                | 1 year           | All cause death, ACS, stroke and unplanned coronary revascularisation exclusive of events related to the culprit lesion. | ICBI ≥43 | 5.16 [1.73 - 15.42] | -     | -     |
| LRP                  |              | 1,563              | 2 years          | Cardiac death or arrest, ACS, revascularisation, readmission for angina and >20% DS progression on angiography. | maxLCBI ≥400 | 1.89 [1.26 - 2.83] | -     | -     |

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, TCF A = thin cap fibroatheroma.
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 personalised therapy and aggressive treatment of these patients with novel medications that appear to improve outcomes in vulnerable populations.\(^{51}\)

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.\(^{52,53}\) The LRP registry included 1,563 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 2 major coronary arteries with length >50mm. At 2-year follow-up, patients with increased lipid burden (4mm lipid core burden index, maxLCBI\(_{4mm} > 400\) 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 maxLCBI\(_{4mm} > 400\) was an 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 synergistic value of NIRS and IVUS in predicting events as IVUS analysis was not complete but restricted to the 4mm segment with the maxLCBI.

The CLIMA study was a prospective multicentre registry that investigated the prognostic implications of OCT-derived plaque characteristic in 1,003 patients who had coronary angiography for clinical purposes and OCT imaging of the untreated proximal left anterior descending coronary artery.\(^{55}\) In this study, a minimum lumen area <3.5mm\(^2\), a lipid arc >180°, a fibrous cap thickness <75μm, and the presence of macrophage accumulations were independent predictors of the combined 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

Summarising the results of these studies and taking into consideration the findings of previous reports, it appears that plaque characteristics provide 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.\(^{54}\) In addition, during this year the first in man application of a polarisation-sensitive OCT imaging system was presented; this modality is expected to enable better plaque characterisation and more detailed evaluation of its components.\(^{55}\) Finally, 2 reports have recently examined the efficacy of the attenuation compensation technique, a post-processing methodology that appears able to enhance OCT imaging depth and enables more accurate evaluation of plaque burden in heavily diseased segments.\(^{54,57}\) 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 destabilisation. In 2019, an analysis of the Integrated Biomarkers Imaging Study 4 (IBIS-4) showed 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.\(^{58,59}\) 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 that describes the existing methodologies and their value for research and possibly clinical practice in the future.\(^{60}\)

### 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 revascularisation. Conversely, an initially conservative management in patients with an out of hospital cardiac arrest without clinical evidence of ongoing 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 revascularisation. 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 personalised pharmaco-invasive strategies.

Conflict of interest: A.B. has received institutional research support from Abbott Vascular and honoraria from Astra Zeneca, Sinomed, Microport, Abbott Vascular, Cardinal Health, and KSH. C.V.B. has no conflict to declare. P.W.S. reports personal fees from Biosensors, Micel Technologies, Sinomedical Sciences Technology, Philips/Volcano, Xeltis, and HeartFlow, outside the submitted work. W.W. has received speaker fees from Biotronik, MicroPort and Terumo; institutional research grants from Abbott Vascular; MiCell, MicroPort and Terumo; was a Medical Advisor for Rede Optimus Research and co-founder of Argonauts Partners, an innovation facilitator.

**FIGURE 5:** Summary of the important clinical studies published in the field in 2019 that will have an impact on the clinical practice.

AF = atrial fibrillation, BRS = bioresorbable scaffold, CTO = chronic total occlusion, DES = drug-eluting stent, ISR = in stent restenosis, IVUS = intravascular ultrasound, OFR = optical coherence tomography-based fractional flow reserve software, STEMI = ST elevation myocardial infarction, vFFR = vessel fractional flow reserve software.
REFERENCES

1. Lemkes JS, Janssens GN, van der Hooven NW, et al. Coronary angiography after cardiac arrest without ST-segment elevation. N Engl J Med 2019; 380:1397-1407.

2. Mehta SR, Wood DA, Storey RF, et al.; COMPLETE Trial Steering Committee and Investigators. Complete revascularisation with multivessel PCI for myocardial infarction. N Engl J Med 2019;381:1411-1421.

3. Patel KK, Spernes JA, Chan PS, et al. Extent of myocardial ischaemia on positron emission tomography and survival benefit with early revascularisation. J Am Coll Cardiol 2019;74:1645-1654.

4. Wintraub WS, Hanighen PM, Marcini GB, et al. Effect of coronary anatomy and myocardial ischaemia on long-term survival in patients with stable ischaemic heart disease. Circ Cardiovasc Qual Outcomes 2019;12:e005079.

5. Hochman JS. International Study of Comparative Health Effectiveness With Medical and Invasive Approaches (ISCHEMIA): Primary report of clinical outcomes. American Heart Association Scientific Sessions 2019, Philadelphia 2019; Nov 16-18.

6. Panza JA, Ellis AM, Al-Khalidi HR, et al. Myocardial viability and long-term outcomes in ischemic cardiomyopathy. N Engl J Med 2019;381:739-748.

7. Neumann F.J, Sousa-Uva M, Ahlsson A, et al.; ESC Scientific Document Group. 2018 ESC/EACTS Guidelines on myocardial revascularisation. Eur Heart J 2019;40:487-165.

8. Farkouh ME, Domanski M, Dangas GD, et al.; FREEDOM Follow-On Study Investigators. Long-term survival following multivessel revascularisation in patients with diabetes: The FREEDOM Follow-On Study. J Am Coll Cardiol 2019;73:629-638.

9. Thuijs DJFM, Kappetein AP, Serruys PW, et al.; SYNTAX Extended Survival Investigators. Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial. Lancet 2019;394:1325-1334.

10. Stone GW, Kappetein AP, Sabik JF, et al.; EXCEL Trial Investigators. Five-year outcomes after PCI or CABG for left main coronary disease. N Engl J Med 2019;381:1820-1830.

11. Stone GW, Sabik JF, Serruys PW, et al.; EXCEL Trial Investigators. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 2016;375:2223-2235.

12. Milosevic M, Serruys PW, Sabik JF 3rd, et al. Bypass surgery or stenting for left main coronary artery disease in patients with diabetes. J Am Coll Cardiol 2019;73:1616-1628.

13. Chen X, Li X, Zhang JJ, et al.; DKCRUSH-V Investigators. 3-year outcomes of the DKCRUSH-V trial comparing DK crush with provisional stenting for left main coronary artery disease in patients with diabetes: The FREEDOM Follow-On Study. J Am Coll Cardiol 2019;73:629-638.

14. Fanou M, Lassen JF, Buszotta F, et al. Percutaneous coronary intervention for obstructive biliary lesions: The 14th consensus document from the EuroCTO Club. EuroIntervention 2019;15:87-165.

15. Galassi AR, Werner GS, Boukris M, et al. Percutaneous recanalisation of non-vitamin K antagonist oral anticoagulant-based randomised clinical trials (DAEDALUS study). Eur Heart J 2021;doi: 10.1093/eurheartj/ehz594.

16. Raber L, Yamaji K, Kelbaek H, et al. Five-year clinical outcomes and intra-coronary imaging findings of the COMFORTABLE AMI trial: Randomised comparison of biodegradable polymer-based biolimus-eluting stents with bare-metal stents in patients with acute ST-segment elevation myocardial infarction. Eur Heart J 2019;40:1909-1919.

17. Glatzer M, Hanrath P, Twardowski H, et al. Biodurability of sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSUTURE): A single-blind, prospective, randomised superiority trial. Lancet 2019;394:1243-1253.

18. Zaman A, de Winter RJ, Kogane N, et al.; TALENT trial investigators. Safety and efficacy of a sirolimus-eluting coronary stent with ultra-thin strut for treatment of atherothrombotic lesions (TALENt): A prospective multicentre randomised controlled trial. Lancet 2019;393:87-99.

19. Stone GW, Kimura T, Gao R, et al. Time-varying outcomes with the absorb bioreabsorbable vascular scaffold during 5-year follow-up: A systematic meta-analysis and individual patient data pooled study. JAMA Cardiol 2019;doi: 10.1001/jamacardio.2019.4101.

20. Bouma NT, Zhang Y, Garg S, et al. Prophylactic implications of coronary calcification in patients with obstructive coronary artery disease treated by percutaneous coronary intervention: A patient-level pooled analysis of 7 contemporary stent trials. Heart 2019;105:1581-1584.

21. Dini CS, Tomberli B, Mattesini A, et al. Intravascular lithotripsy for calcific coronary and peripheral artery stenoses. EuroIntervention 2019;15:714-721.

22. Brinton Tj, Ali ZA, Hill JM, et al. Feasibility of shockwave coronary intravascular lithotripsy for the treatment of calcified coronary stenoses. Circulation 2019;139:e384-386.

23. Ali ZA, Nef H, Escaned J, et al. Safety and effectiveness of coronary intravascular lithotripsy for treatment of severely calcified coronary stenoses: The disrupt CAD II study. Circ Cardiovasc Interv 2019;12:e008434.

24. Wilson Sj, Spratt JC, Hill J, et al. Coronary intravascular lithotripsy is associated with a high incidence of “shocktopics” and asynchronous cardiac pacing. EuroIntervention 2019;15:1091-1096.

25. Mehran R, Baer F, Sharma SK, et al. Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med 2019;381:2032-2042.

26. Costa F, Van Klaveren D, Feres F, et al.; PRECISE-DAPT Study Investigators. Dual antiplatelet therapy duration based on ischemic and bleeding risks after coronary stenting. J Am Coll Cardiol 2019;73:741-754.

27. Lopes RD, Heizger G, Aronson R, et al. Antithrombotic therapy after Acute Coronary Syndrome or PCI in atrial fibrillation. N Engl J Med 2019;380:1509-1524.

28. Vranckx P, Valimigil M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): A randomised, open-label, phase 3b trial. Lancet 2019;394:1335-1343.

29. Gargiulo G, Goette A, Tijssen J, et al. Safety and efficacy outcomes of double versus single drug eluting stent for the treatment of coronary in-stent restenosis: A comprehensive, collaborative, individual patient data meta-analysis of 10 randomised clinical trials (DAEDELUS study). Eur Heart J 2021;doi: 10.1093/eurheartj/ehz594.

30. Raber L, Yamaji K, Kelbaek H, et al. Five-year clinical outcomes and intra-coronary imaging findings of the COMFORTABLE AMI trial: Randomised comparison of biodegradable polymer-based biolimus-eluting stents with bare-metal stents in patients with acute ST-segment elevation myocardial infarction. Eur Heart J 2019;40:1909-1919.

31. Glatzer M, Hanrath P, Twardowski H, et al. Biodurability of sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSUTURE): A single-blind, prospective, randomised superiority trial. Lancet 2019;394:1243-1253.

32. Zaman A, de Winter RJ, Kogane N, et al.; TALENT trial investigators. Safety and efficacy of a sirolimus-eluting coronary stent with ultra-thin strut for treatment of atherothrombotic lesions (TALENt): A prospective multicentre randomised controlled trial. Lancet 2019;393:87-99.

33. Stone GW, Kimura T, Gao R, et al. Time-varying outcomes with the absorb bioreabsorbable vascular scaffold during 5-year follow-up: A systematic meta-analysis and individual patient data pooled study. JAMA Cardiol 2019;doi: 10.1001/jamacardio.2019.4101.

34. Bouma NT, Zhang Y, Garg S, et al. Prophylactic implications of coronary calcification in patients with obstructive coronary artery disease treated by percutaneous coronary intervention: A patient-level pooled analysis of 7 contemporary stent trials. Heart 2019;105:1581-1584.

35. Dini CS, Tomberli B, Mattesini A, et al. Intravascular lithotripsy for calcific coronary and peripheral artery stenoses. EuroIntervention 2019;15:714-721.

36. Brinton Tj, Ali ZA, Hill JM, et al. Feasibility of shockwave coronary intravascular lithotripsy for the treatment of calcified coronary stenoses. Circulation 2019;139:e384-386.

37. Ali ZA, Nef H, Escaned J, et al. Safety and effectiveness of coronary intravascular lithotripsy for treatment of severely calcified coronary stenoses: The disrupt CAD II study. Circ Cardiovasc Interv 2019;12:e008434.

38. Wilson Sj, Spratt JC, Hill J, et al. Coronary intravascular lithotripsy is associated with a high incidence of “shocktopics” and asynchronous cardiac pacing. EuroIntervention 2019;15:1091-1096.
37. Warisawa T, Cook CM, Howard JP, et al. Physiological pattern of disease assessed by pressure-wire pullback has an influence on fractional flow reserve/instantaneous wave-free ratio discordance. Circ Cardiovasc Interv 2019;12:e00749J.

38. Lee SH, Choi KH, Lee JM, et al. Physiologic characteristics and clinical outcomes of patients with discordance between FFR and iFR. JACC Cardiovasc Interv 2019;12:2018-2031.

39. Sen S, Ahmad Y, Dehbi HM, et al. Clinical events after deferral of LAD revascularisation following physiological coronary assessment. J Am Coll Cardiol 2019;73:444-453.

40. DEFINE-FLAIR Trial Investigators, Lee JM, Choi KH, et al. Comparison of major adverse cardiac events between instantaneous wave-free ratio and fractional flow reserve-guided strategy in patients with or without type 2 diabetes: A secondary analysis of a randomised clinical trial. J Am Coll Cardiol 2019;doi: 10.1001/jamacardio.2019.2298.

41. Masjedi K, van Zandvoort LC, Balbi MM, et al. Validation of 3-dimensional quantitative coronary angiography-based software to calculate fractional flow reserve: Fast Assessment of STenosis severity (FAST)-study. EuroIntervention 2019;doi: 10.4244/EIJ-D-19-00466.

42. Yu W, Huang J, Jia D, et al. Diagnostic accuracy of intracoronary optical coherence tomography-derived fractional flow reserve for assessment of coronary stenosis severity. EuroIntervention 2019;15:189-197.

43. Gao XF, Wang ZM, Wang F, et al. Intravascular ultrasound guidance reduces cardiac death and coronary revascularisation in patients undergoing drug-eluting stent implantation: Results from a meta-analysis of 9 randomised trials and 4724 patients. Int J Cardiovasc Imaging 2019;35:239-247.

44. Hong MK. IVUS-XPL: 5-year outcomes from a randomised trial of intravascular ultrasound-guided vs. angiography-guided PCI of long coronary lesions. FORZA: A Randomised Trial of Fractional Flow Reserve vs. Optical Coherence Tomography to Guide Revascularisation of Intermediate Coronary Stenoses. Transcatheter Cardiovascular Therapeutics; San Francisco, CA; 25-29 Sept 2019.

45. Buzotta F. Transcatheter Cardiovascular Therapeutics; San Francisco, CA; 25-29 Sept 2019.

46. Johnson TW, Raber L, di Mario C, et al. Clinical use of intracoronary imaging. Coherence Tomography to Guide Revascularisation of Intermediate Coronary Stenoses. Transcatheter Cardiovascular Therapeutics; San Francisco, CA; 25-29 Sept 2019.

47. Knutsen J, Wijns W, Saraste A, et al.; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019; doi: 10.1093/ehjcvjz.85.

48. Nagel E, Greenwood JP, McGinn GP, et al; MR-INFORM Investigators. Magnetic resonance perfusion or fractional flow reserve in coronary disease. N Engl J Med 2019;380:2418-2428.

49. Calvino-Santos R, Estevez-Loureiro R, Peitero-Vazquez J, et al. Angiographically guided complete revascularisation versus selective stress echocardiography-guided revascularisation in patients with ST-segment-elevation myocardial infarction and multivessel disease: The CROSS-AMI randomised clinical trial. Circ Cardiovasc Interv 2019;12:e007924.

50. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364:226-235.

51. Bourantas CV, Garcia-Garcia HM, Torri R, et al. Vulnerable plaque detection: An unrealistic quest or a feasible objective with a clinical value? Heart 2016;102:581-589.

52. Wakamori R, Di Mario C, Torguson R, et al. Identification of patients and plaques vulnerable to future coronary events with near-infrared spectroscopy intravascular ultrasound imaging: A prospective, cohort study. Lancet 2019;394:1629-1637.

53. Prati F, Romagnoli E, Gatto L, et al. Relationship between coronary plaque morphology of the left anterior descending artery and 12 months clinical outcome: The CLIMA study. Eur Heart J 2020;41:383-391.