



# The year in cardiology 2016: coronary interventions

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## Preamble

2016 can be hardly described as a year of revolutions in interventional cardiology. Still multiple randomized studies supported the 3 to 5 year efficacy of metallic drug eluting stents in left main disease, cast doubts on long-term outcome after fully biodegradable stents, discouraged routine thrombectomy during primary PCI, gave a mixed message on the importance of physiological guidance of coronary revascularization, helpful for non-culprit lesions in STEMI, questionable for multivessel disease in allcomers, and defeated the paradigm that a fully arterial surgical revascularization delivers better clinical outcome.

## Myocardial revascularization

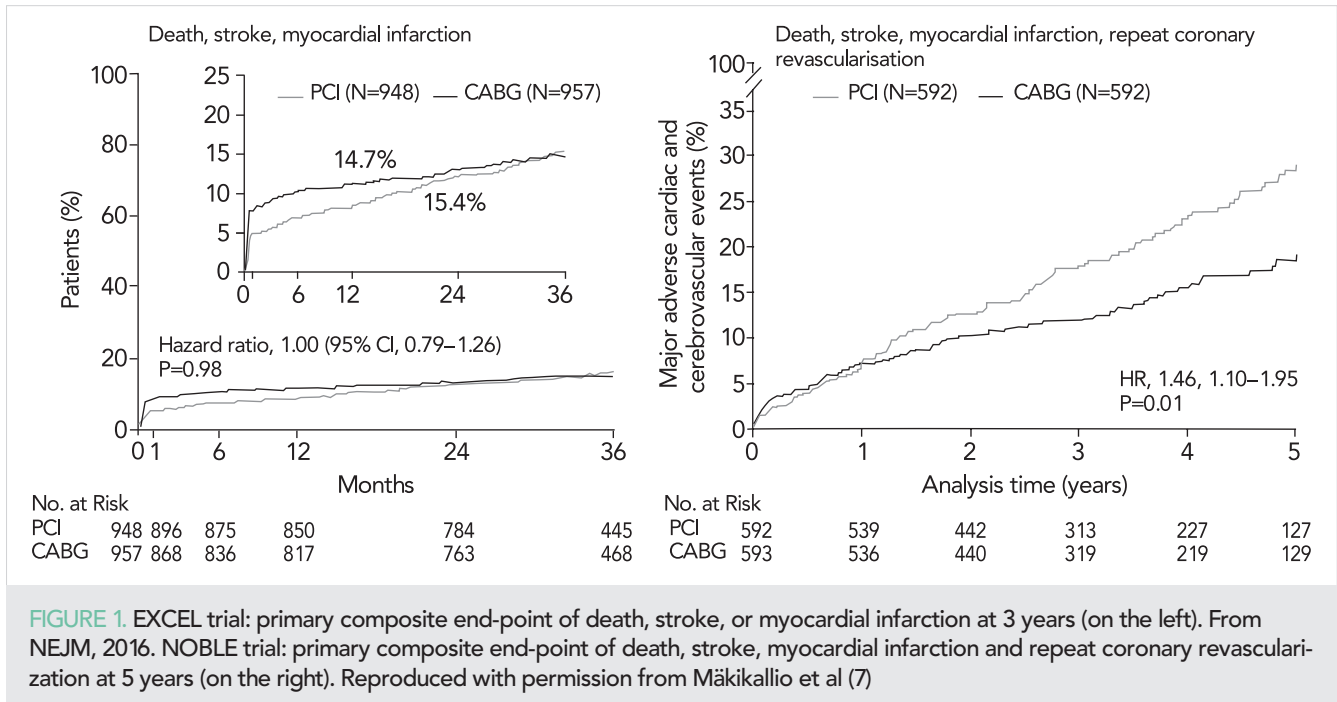
### Revascularization vs. medical therapy

We start this review of transcatheter interventions with a trial where bypass surgery rather than stent-assisted angioplasty was used and compared with medical therapy. STICH (1) (Surgical Treatment for Ischemic Heart Failure) compared optimal medical therapy (OMT) and surgical revascularization with coronary artery by-pass grafting (CABG) in 1215 patients with left ventricular ejection fraction (LVEF)  $\leq 35\%$ . The negative results at 4.8 years of the original presentation in 2010 (death from any cause in 41% of patients in OMT and 36% in the CABG group,  $P=0.12$ ) justified the conservative attitude of our heart failure colleagues towards myocardial revascularization. In 2010–2013, in USA only 17.5% of 67 161 patients hospitalized for new onset heart failure underwent testing for ischemic CAD during the index hospitalization (2). The highlight of the Europe-

an Society of Cardiology Congress 2016 in Rome was the presentation of the results at 9.8 years of STICHES (3) (Surgical Treatment for Ischemic Heart Failure Extension Study), showing progressive divergence of the curves for mortality (66.0% in OMT group vs. 58.9% in the CABG group,  $P=0.02$ ) and cardiovascular mortality (49.3% vs. 40.5%, respectively,  $P=0.006$ ), with a significant difference in favour of the surgical arm. In the CABG group, the NNT to prevent one death was 14, though mortality was high in both groups. This trial has implications for transcatheter myocardial revascularization as well because surgery often has a prohibitive risk in patients with very low LVEF and angioplasty with drug eluting stents (DES) may represent a valid alternative in selected patients.

### CABG technique

There is clear evidence of excellent long-term patency of the left internal mammary artery on the left anterior descending artery (LAD) with greater late mortality in patients only receiving vein grafts. Fully arterial revascularization is expected to improve the long-term results of CABG and this may have implications for trials comparing CABG and PCI with DES which typically have a rate of utilization of bilateral mammary of  $<25\%$ . In the recent ART trial (4) (Arterial Revascularization Trial), 3102 patients treated with CABG were randomized to single internal-thoracic-artery grafting or bilateral-internal thoracic-artery grafting. After 5 years of follow-up, no differences in mortality rate (8.5% in bilateral arterial graft group vs. 8.4% in single graft group,  $P=0.77$ ) were observed. In addition, death from any cause, myocardial infarction (MI) or stroke was similar in the two groups (12.2% vs. 12.7%, respectively). As already



shown in the 1 year follow-up report, wound infections and need for sternal reintervention were higher in the bilateral mammary group (P=0.005 and P=0.002).

**PCI vs. CABG in diabetes**

In the choice between PCI and CABG appropriate patient selection appears the key factor. In 451 patients with diabetes mellitus and renal failure (GFR <60 ml/min) presented in a subanalysis of the FREEDOM trial (5) (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease), CABG was shown to be superior to percutaneous coronary intervention (PCI) in major adverse cardiovascular and cerebral events (MACCE), particularly in terms of rates of spontaneous MI (HR 0.27, CI 95%: 0.11–0.65) and repeat revascularization (HR 0.30, IC 95%: 0.18–0.50).

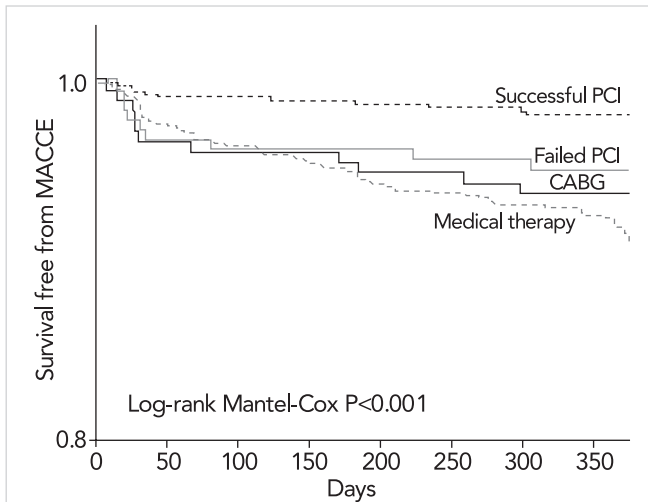
**PCI vs. CABG for left main disease**

Two trials, EXCEL (6) (evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) and NOBLE (7) (NOrdic-Baltic-British LEft main revascularization), randomly compared PCI and CABG in 1905 and 1201 patients, respectively. The different results of the two trials are likely explained by differences in the stents used (the first generation Cypher and Biomatrix in NOBLE and the second generation everolimus eluting XIENCE stent in EXCEL) and in the prespecified components of the primary end-point (new revascularization in NOBLE, periprocedural large MI in EXCEL). At 3 years median follow-up EXCEL confirmed and improved the results of PCI in the left main (LM) subset of the SYNTAX trial, showing a clear non-inferiority of PCI vs. surgery in pa-

tients with low to intermediate disease burden (SYNTAX score ≤33) and critical LM disease (incidence of the combined end-point of death from any cause, MI or stroke was 15.4% in the PCI group vs. 14.7% in the CABG group; P=0.02 for non-inferiority). PCI enthusiasts will claim that lower initial mortality, stroke and large MI and the absence of periprocedural surgical complications (bleeding, infections, major arrhythmias, present in 3.7%, 2.5% and 2.1% of the CABG patients, respectively) are sufficient reasons to prefer PCI over surgery. A more balanced view will stress the equalization of late results in the Kaplan–Meier curves for the MACCEs included in the primary end-point. The initial advantage of PCI is lost at 3 years in EXCEL, when the two curves cross each other, and there is more frequent revascularization in the PCI group (12.6% vs. 7.5% in the CABG group, P<0.01). Still revascularization and stent thrombosis (0.7%) were much lower than in SYNTAX, while the incidence of symptomatic graft occlusion was similar in EXCEL and SYNTAX (5.4% and 4.2%, respectively). NOBLE showed an unexpectedly low incidence of stroke in the surgical arm, particularly in the first weeks and an inferiority of PCI vs. CABG when revascularization is included in the primary end-point (29% for PCI vs. 19% for CABG, P=0.006) (Figure 1), with a statistically non-significant mortality difference in favour of surgery at 5 years (12% in PCI group vs. 9% in CABG group, P=0.77).

**CTO treatment**

Van der Schaaf et al. (8) were the first to demonstrate that patients with ST-elevation myocardial infarction (STEMI) and a second occluded artery had a much worse prognosis, results later confirmed by many other



**FIGURE 2.** Kaplan–Meier analysis of freedom from major adverse cardiac and cerebrovascular events in patients with successful PCI, failed PCI, patients managed with OMT or CABG, before propensity score adjustment. Reproduced with permission from Tomasello et al (12)

registries and subanalysis of randomized trials (HORIZONS) (9). The EXPLORE trial (10) (Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Segment Elevation Myocardial Infarction), enrolled 304 STEMI patients with coronary total occlusion (CTO) in a non-culprit vessel and randomized them to receive recanalization within 7 days from primary PCI or to culprit lesion treatment alone. The primary end-point of LVEF and end-diastolic volume (EDV) at 4 months post-MI was negative (LVEF:  $44.1 \pm 12.2\%$  in the CTO PCI arm vs.  $44.8 \pm 11.9\%$  in the conservative arm,  $P=0.60$ ) with a favourable difference in favour of PCI only in patients receiving treatment of a CTO of the LAD.

This result, the first reported of three randomized trials addressing the prognostic value of CTO treatment (the EuroCTO trial and a similar size Korean study have both completed enrolment last year), contradicts the outcome of many large registries showing a favorable outcome of successful CTO recanalization. This was confirmed in the 14 441 patients included in the SCAAR registry (11) (Swedish Coronary Angiography and Angioplasty Registry) in the period 2005–2012. The presence of a CTO was an independent predictor of long term mortality (HR 1.29, 95% CI: 1.22–1.37,  $P<0.01$ ), with an average mortality increase of 6.6% each year. Successful CTO recanalization (54% of 6442 patients underwent PCI for CTO) was associated with a reduced mortality risk (HR 0.85, 95% CI: 0.73–0.98,  $P<0.034$ ). In an Italian multicenter registry (12) (IRCTO), 776 patients (43.7%) were treated with PCI, showing lower mortality rate at 1 year than the patients on OMT or undergoing surgical revascularization (1.4% PCI vs. 4.7% and 6.3% surgery and medical therapy, respectively; both  $P<0.001$ ) and lower MACCE (2.6% vs. 8.2% and

6.9%,  $P<0.001$ ) (Figure 2). Registry data have obvious drawbacks and the most important is that they do not consider the entire population of the patients treated but only the 60–70% that typically achieve successful procedures. While waiting for the results of true randomized trials including in the CTO group all the patients with attempted recanalization (intention to treat), it is encouraging to see a progressive improvement of success rate (80–90%) in large consecutive registries. The RECHARGE (13) registry (REgistry of Crossboss and Hybrid procedures in FrAnce, NetheRlands, BelGium and UnitEd Kingdom) analysed 1177 patients with CTO (59% lesion length > 20 mm, 58% calcific lesions, J-CTO score  $2.2 \pm 1.3$ ) and showed a high overall procedure success (86%) following a hybrid algorithm (anterograde wire escalation 77%, retrograde dissection re-entry 17% and anterograde dissection re-entry 7%). Major in-hospital complications were low (2.6%) with very low periprocedural mortality (0.2).

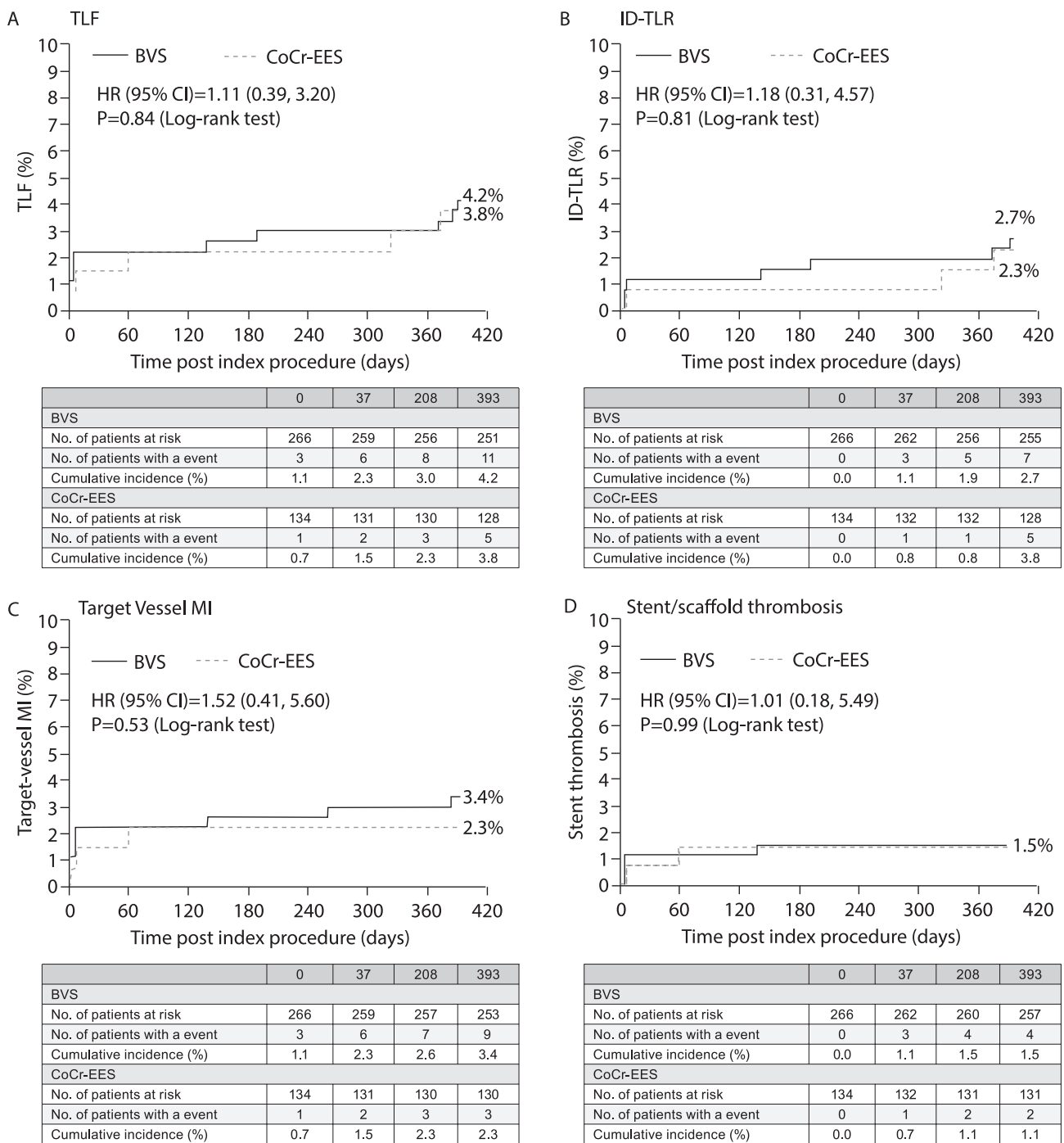
### Bifurcations

The guidelines (14) recommending provisional stenting as default strategy in bifurcational lesions were supported by results of 5 year survival of a patient level pooled analysis of two randomized trials (15). In both studies, 500 patients in the BBC-ONE trial (British Bifurcation Coronary study One) and 413 patients in the NORDIC trial (Nordic Bifurcation study) were randomly assigned to provisional stent or a two-stent approach with the first generation drug eluting stents (DES) Cypher and Taxus. Five year mortality was lower among patients who underwent a provisional strategy, 17 patients (3.8%) vs. 31 patients (7.0%) in the two-stent strategy ( $P<0.04$ ). When a second stent is required, the Bifurcation Bad Krozingen (16) (BBK) randomized trial showed that the two most widely used techniques applicable in a provisional fashion (T-stenting and culotte) deliver different results, with a significantly lower maximal in-stent % diameter stenosis at angiographic follow-up ( $P<0.038$ ) and lower binary restenosis at 1 year follow-up in the 150 patients treated with culotte than in the equal number of patients receiving T-stenting (6.5% vs. 17.0%,  $P=0.006$ ). The clinical relevance of these findings is challenged by the absence of significant differences in TLR between the two groups (6% in culotte group vs. 12% in TAP group,  $P=0.069$ ). This trial that utilized modern second generation DES had excellent overall results, and only one stent thrombosis at 1 year.

### Acute coronary syndromes

#### Thrombectomy for STEMI

The TOTAL trial (17) (ThrOmbecTomy with percutaneous coronary intervention vs. PCI ALone in patients with ST-elevation myocardial infarction undergoing primary PCI) is a large multicenter trial where patients



**FIGURE 3.** Primary and secondary end-points: (A) target lesion failure, (B) ischemia driven TLR, (C) target vessel MI, (D) stent or scaffold thrombosis in Absorb Japan trial. Reproduced with permission from Kimura et al (40)

with STEMI were randomized to manual thrombectomy and PCI or PCI alone. The absence of any evidence of improved prognosis at 30 days with the routine use of manual thrombectomy was confirmed at 1 year, with a small but worrisome increase in neurological events in patients receiving manual thrombectomy (1.2% vs. 0.7%,  $P=0.015$ ). In the angiographic sub-study of the TOTAL trial (18), routine thrombectomy did not impro-

ve final MBG (myocardial blush grading) or TIMI flow (thrombolysis in myocardial infarction) when compared with PCI alone, but it was associated with a decreased rate of distal embolization (7.1% in thrombectomy group vs. 10.7% in PCI alone group,  $P<0.01$ ), a complication confirmed as an independent predictor of mortality (HR 3.00, 95% CI: 1.19–7.58). These two articles confirmed the recent change in the US and European revascu-



larization and STEMI guidelines that discouraged the routine use of manual thrombectomy (14, 19) in primary PCI.

### **STEMI, immediate vs. deferred stent implantation**

The Danish registry DANAMI (DANish Study of Optimal Acute Treatment of Patients With ST-elevation Myocardial Infarction) analysed 3854 patients in the period 2011–2014. In the DANAMI-3-DEFER (20), 1215 patients were randomized to receive standard primary PCI with immediately stent implantation or deferred stent implantation (median of 3 days) to reduce the risk of embolization and no-reflow phenomenon. The primary end-point, a composite of all-cause mortality, hospital admission for heart failure, recurrent infarction, and unplanned TLR, was similar in the two groups (18% in immediate PCI, 17% in deferred PCI,  $P=0.92$ ). Distal embolization was observed in <10% and was equal in the two groups (but crossover from deferred to immediate stent implantation was frequent, occurring in 22% of cases).

### **Non-culprit lesion treatment in STEMI**

The multicenter randomized DANAMI-3 PRIMULTI (21) trial addressed the recurrent question of the optimal treatment of critical lesions in non-culprit vessels in 627 patients undergoing primary PCI. FFR-guided complete revascularization during the initial hospitalization of patients with STEMI and multivessel disease improved outcome after 2 years of follow-up. Mortality and non-fatal MI were similar in the two groups but ischemia-driven repeat revascularization was 69% lower in the FFR guided group (17.0% vs. 5.0%,  $P<0.0001$ ). This result suggests that a delayed in-hospital FFR guided revascularization should be preferred to a conservative symptoms guided strategy.

### **Timing of PCI in NSTEMI**

The European guidelines (22) recommend coronary angiography and possible PCI within 24 h from hospital admission in patients with positive troponin or ischemic ECG changes. In the RIDDLE-NSTEMI trial (23) (Immediate Versus Delayed Invasive Intervention for Non-STEMI Patients), 323 patients with NSTEMI were randomized to immediate intervention (<2 h) and delayed intervention (2–72 h). At 30 days, mortality and new MI were lower in the immediate intervention group (4.3% vs. 13%,  $P=0.008$ ), a difference that was confirmed at 1 year (6.8% vs. 18.8%,  $P=0.002$ ).

### **PCI in out-of-hospital cardiac arrest (OHCA)**

The optimal timing of coronary angiography is unclear in patients with OHCA and without ST-elevation. In the PROCAT II (24) registry (Parisian Region Out of hospital Cardiac Arrest), 695 patients after OHCA without ST elevation and without extracardiac causes of the event

underwent emergency coronary angiography (immediate transfer to cath lab like for primary angioplasty). In 403 patients (58%), at least one significant coronary lesion was observed and in 199 patients (29%), emergency PCI was performed. Successful recovery was observed in 43% of patients after emergency PCI and 33% of patients treated conservatively, with successful PCI emerging as an independent predictor of recovery (HR 1.8, 95% CI: 1.09–2.97,  $P=0.02$ ).

### **ACS in elderly patients**

Patients older than 80 years with ACS are quickly increasing as a consequence of the aging world population but these patients are underrepresented in clinical trials and undertreated with invasive and pharmacological therapy. In the EIGHTY trial (25), 457 octogenarians were randomized to invasive treatment or medical treatment. After 1.53 years of follow-up, the combined primary end-point of death, MI, urgent revascularization and stroke occurred in 40.6% of invasive group vs. 61.4% of conservative group ( $P=0.001$ ), with significant differences for MI and urgent revascularization. No differences in bleeding complications were observed.

### **Routine follow-up angiography after PCI**

The REACT trial (26) (Randomized Evaluation of Routine Follow-up Coronary Angiography after Percutaneous Coronary Intervention) investigated the value of routine coronary angiography 9–12 months after the initial angioplasty, a practice widely used in all patients in Japan and reserved outside Japan to selected subgroups such as LM or diffuse disease in diabetic patients. Unfortunately, the trial enrolled only 700 out of the 3300 originally planned patients which precludes meaningful subgroup subanalysis. Results showed a 15% increase in revascularization as a consequence of the follow-up angiogram, not translating into a reduction of MI or mortality at 5 years follow-up. The result discourages routine use of diagnostic angiography but also shows that over the first 5 years, the conservative group reaches the same revascularization rate, a clinically mandated catch-up phenomenon that partially justifies the clinical value of elective early retreatment.

## **Devices**

### **Bare metal stent (BMS) vs. drug eluting stent (DES)**

The universal use of DES was challenged by the results of the NORSTENT trial (27) (Norwegian Coronary Stent Trial), a randomized multicenter comparison of BMS vs. DES (82.9% everolimus-eluting stents and 13.1% zotarolimus-eluting stents) in 9013 Norwegian patients. The study excluded, among others, patients with previous coronary stenting or with bifurcation lesions requiring treatment with a two-stent technique. Mortality and spontaneous MI, the primary end-point of the trial, were

similar in the two groups at 6 years (median follow-up 59 months). The DES group showed a reduction in target lesion revascularization (TLR) (19.8% in BMS group vs. 16.5% in DES group,  $P < 0.001$ ). The number needed to treat to prevent one repeat revascularization (NNT=30) was high in comparison to previous DES studies but low when compared with the typical NNT of pharmacological studies. Concerns about high cost could have deterred doctors from using DES 5 years ago when DES were much more expensive than BMS. This smaller than expected difference is unlikely to have an impact now, especially in the absence of any signal of possible increase of late in-stent thrombotic events (in fact there was a small but significant difference in favour of DES, definite or probable ST was 1.2% in the BMS group and 0.8% in the DES group,  $P = 0.0498$ ).

For many years, BMS were preferred in patients at high risk of bleeding to avoid the need of a prolonged double antiplatelet therapy or, worse, triple antiplatelet/antithrombotic therapy. Recently, this practice has been challenged by the availability of data showing safety of early withdrawal of dual antiplatelet therapy (DAPT) in patients treated with second generation zotarolimus or everolimus eluting stents. In the randomized multicenter LEADERS-FREE trial (28) better results were obtained with a polymer free biolimus A9 (umirolium) DES used with only 1 month of DAPT in comparison with BMS. The significant reduction of TLR observed at 1 year (5.1% in DES group vs. 9.8% in BMS group,  $P < 0.01$ ) was confirmed at 2 years (29) (6.8% in DES group vs. 12.0% in BMS group,  $P < 0.001$ ). In addition, a post hoc analysis of the LEADERS FREE trial confirmed these results in 1575 elderly patients (30) (>75 years). The composite safety end-point of cardiac death, MI and ST was reached in 14.3% of the BMS group and 10.7% of the DES group, ( $P = 0.03$ ). In addition, the primary end-point of clinically driven TLR was worse in the BMS group (10.8%) than in the DES group (5.8%,  $P < 0.01$ ). The pre-specified subanalysis of the ZEUS trial (31) (Zotarolimus Eluting Endeavor Sprint Stent in Uncertain DES Candidates) showed that MACE were lower in high risk bleeding patients treated with zotarolimus eluting stent than in BMS patients (22.6% in DES group vs. 29.0% in BMS group,  $P > 0.01$ ). A prespecified post hoc analysis of the PRODIGY trial (32) (PROlonging Dual antiplatelet treatment after Grading stent-induced Intimal hyperplasia study), analysed 323 patients with chronic renal failure (eGFR < 60 ml/min/1.73 m<sup>2</sup>) with stable coronary disease or ACS undergoing PCI. It showed a lower risk of stent thrombosis and lower MACE rate at 2 years in patients treated with everolimus or zotarolimus eluting stent than in patients treated with paclitaxel eluting stents or BMS.

#### Late follow-up after DES

The SIRTAX-very late trial (33) (Sirolimus-Eluting vs. Paclitaxel-Eluting Stents for Coronary Revasculariza-

tion) reported 10 year results of a Swiss randomized comparison study between sirolimus eluting (CYPHER) and paclitaxel eluting stents (TAXUS). The fear was that a continuous progression of late lumen loss and the development of accelerated neoatherosclerosis in DES could induce a poor long-term outcome. Results showed that the annual risk of TLR between 5 and 10 years was >60% lower than in the period between 1 and 5 years (0.7%/year vs. 1.8%/year,  $P < 0.001$ ). Equally, the annual risk of very late stent thrombosis decreased during the extended follow-up period (5–10 years: 0.23%/year vs. 1–5 years: 0.67%/year,  $P < 0.01$ ). In the ISAR-Test 5 trial (34) (Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus and Probucol and Zotarolimus Eluting Stents), 3,002 patients were randomly assigned to treatment with polymer-free sirolimus- and probucol-eluting stents ( $n = 2002$ ) or Resolute stent (biostable polymer eluting zotarolimus,  $n = 1000$ ). The 5 year follow-up confirmed the non-inferiority of the first group for a composite of cardiac death, target-vessel related myocardial infarction, or TLR (23.8% vs. 24.2%,  $P = 0.80$ ). Stent thrombosis was low and similar in the two groups (1.3% vs. 1.6%,  $P = 0.64$ ). In the EXAMINATION trial (35) (A Clinical Evaluation of Everolimus Eluting Coronary Stents in the Treatment of Patients With ST-segment Elevation Myocardial Infarction), 1498 patients with STEMI treated with primary PCI were randomly assigned to receive everolimus eluting stent or BMS. After 5 years, a composite end-point of all-cause death, any myocardial infarction, or any revascularization was met in 21% of patients in the EES group vs. 26% in the BMS group ( $P = 0.033$ ), mainly driven by a lower rate of all-cause mortality ( $P = 0.047$ ).

#### Comparison of modern second generation DES

The BIO-RESORT TWENTE III trial (36) compared two third generation DES (sirolimus eluting Orsiro stent and everolimus eluting Synergy) with biodegradable polymer coatings with a second generation durable polymer DES (zotarolimus eluting Resolute Integrity). Results in 3514 all-comer patients showed very low incidence of new revascularization and very low stent thrombosis (0.3%), equivalent for the three platforms ( $P = 0.7$ ). The PRISON IV trial (37) is a randomized, multicenter trial designed to evaluate the safety and efficacy of hybrid sirolimus-eluting stents (SES) with bioresorbable polymer (Orsiro) compared with everolimus-eluting stents (EES) with durable polymers (Xience Prime) after CTO recanalization. In 330 patients analysed in this trial, new generation DES did not meet the non-inferiority criteria for in-segment late lumen loss when compared with second generation DES ( $0.13 \pm 0.63$  mm in SES group vs.  $0.02 \pm 0.47$  mm in EES,  $P$  for superiority = 0.08). In addition, binary restenosis was significantly higher in SES (8.0% in SES vs. 2.1% in EES,  $P = 0.028$ ), while the clinical end-points were similar in both groups.

### Bioresorbable Scaffolds

Four large multicenter randomized trials from Europe (ABSORB II (38), 501 patients), USA (ABSORB III (39), the largest with 2,008 patients), Japan and China (ABSORB Japan (40) and ABSORB China (41), 400 and 480 patients respectively) compared a bioresorbable or a metallic stent eluting everolimus. ABSORB III showed non-inferiority of Absorb vs. Xience in terms of target lesion failure (TLF) at 1 year (7.8% for Absorb vs. 6.1% for Xience,  $P=0.16$ ), cardiac death (0.6% vs. 0.1%,  $P=0.29$ ) and stent thrombosis at 1 year (1.5% vs. 0.7%,  $P=0.13$ ). ABSORB China (41) focused on a primary angiographic end-point of in-segment late loss and showed a low late lumen loss at 1 year ( $0.19 \pm 0.38$  mm) in the Absorb group, non-inferior to the  $0.13 \pm 0.38$  mm observed in the Xience group. Angiographic restenosis at 13 months was low, 1.9% and 3.9% ( $P=0.31$ ) in the Absorb Japan trial (40). In a large patient-level pooled meta-analysis, 3389 patients (42) from four trials with stable coronary disease or ACS were randomized to receive BVS (2164 patients) or metallic EES (1225 patients). No significant differences were observed in the patient oriented composite end-point of all cause mortality, all MI or all revascularization at 1 year, and in the device oriented composite end-point of TLF, including cardiac mortality, target vessel related MI or ischemia driven TLR ( $P=0.17$ ). The most worrisome data came from the 3 year results of the oldest of these studies, ABSORB II (43). Unexpectedly, the primary end-point of vasomotor reactivity did not differ in the two groups (0.047 mm for BVS vs. 0.056 mm for EES,  $P_{\text{superiority}}=0.49$ ). Six patients experienced definite very late scaffold thrombosis in the BVS group (2.0% in total vs. 0% in the XIENCE arm,  $P=0.19$ ), with a higher incidence of clinically indicated TLR (6% vs. 2%,  $P=0.04$ ). While presenting these results, Serruys called for a prolongation of double antiplatelet therapy and suggested a drastic modifications of the protocol of stent implantation recommended in the ABSORB II study, with rare use of imaging and post-dilatation. More fundamental criticisms pointed to the limitations of the current ABSORB platform (strut thickness of 150 micron, low radial force, 0.5 mm margin for further diameter expansion, lack of X-ray visibility), enhancing the interest for the favorable results of initial registries of thinner biodegradable stents. These results are certainly upsetting those cardiologists who believed that an initial greater complexity of implant and a possible price to pay in terms of higher early stent thrombosis was due to be compensated by an absolute absence of late events after the completion of the absorption process. The follow-up duration might be insufficient for a complete absorption of the PLLA when the struts are detached from the wall and gross persistent abnormalities of vascular rheology due to malapposed struts can trigger thrombosis even after complete absorption if intraluminal strands remain.

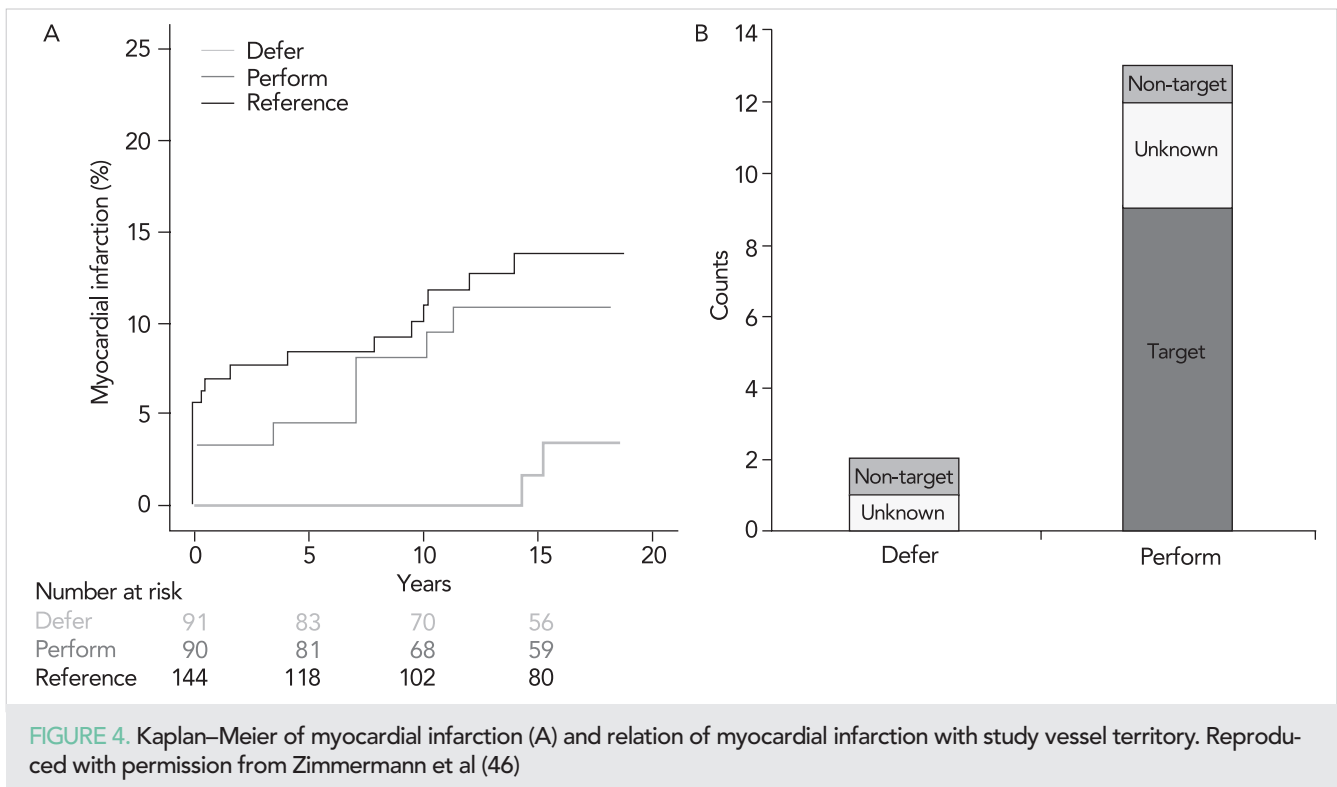
### Other devices

Severe coronary calcification remains a predictor of worse clinical outcomes. In the ORBIT II trial (44) (Evaluate the Safety and Efficacy of Orbital Atherectomy System in Treating Severely Calcified Coronary Lesions), 443 patients with severe calcified lesions were treated with orbital atherectomy for pre-stent implantation preparation. The 2 year follow-up of the ORBIT II trial extended the favorable results previously shown at 30 day and 1 year follow-up: MACE was 19.4%, all-cause death 7.5%, cardiac death 4.3%, and TLR 6.2%. The stratification for stent type showed a worse result in BMS vs. first and second-generation DES (TLR15.1% in BMS vs. 6.3% first-generation DES vs. 5.0% in second-generation DES,  $P=0.047$ ). The DISRUPT CAD trial is the first coronary experience with a lithoplasty balloon (Shockwave Medical) (45), a device previously used only in peripheral vessels. Sixty patients with moderate or severe calcific lesions (stenosis  $>50\%$ , reference vessel diameter 2.5–4.0 mm, lesion length  $<32$  mm) were treated before stenting with excellent stent expansion and OCT documented fractures of superficial calcifications in 58%. This device proved to be safe, with no final angiographic complication and a low 30 day MACE (no death, no Q-wave MI, 5% non-Q MI). Both orbital atherectomy and, especially, the revolutionary approach of lithotripsy of coronary calcium have the potential to greatly improve the effects limited to superficial calcium achieved with Rotablator but, so far, no comparison data are available.

### Functional and imaging guidance

*Fractional flow reserve (FFR) for intermediate lesions*  
DEFER (46) was the first study confirming the clinical usefulness of FFR showing similar freedom from major adverse cardiac events (death, MI, and repeat revascularization), the primary end-point of the trial, withdrawing PCI in patients initially referred for treatment when FFR was  $>0.75$ . The long-term safety of deferring treatment of lesions of intermediate angiographic severity when FFR is above the threshold of 0.75 was confirmed by the 15 years results of the 5 years DEFER trial, conducted in the late-90s in 250 patients using POBA or BMS, and the DEFER DES trial (47), randomizing 229 patients using first or second (70%) generation DES. In DEFER, after a 15 year follow-up, there was still no difference in all-cause mortality among the three groups of randomization (36.1% reference group vs. 33% DEFER vs. 31.1% performance,  $P=0.79$ ). MI was significantly lower in the DEFER group compared with the perform PCI group (2.2% vs. 10%,  $P=0.03$ ), mainly because of a lower target vessel infarction (Figure 4). In DEFER-DES, there was no difference in MACE after 5 year follow-up ( $11.6 \pm 3.0\%$  in the routine-DES group and  $14.2 \pm 3.3\%$  in the FFR-guided group,  $P=0.55$ ). It is obviously dangerous to overemphasize differences in events that were not from the primary end-point of the





**FIGURE 4.** Kaplan–Meier of myocardial infarction (A) and relation of myocardial infarction with study vessel territory. Reproduced with permission from Zimmermann et al (46)

trial and at different times than the planned follow-up. The lack of impact of PCI in DEFER-DES can be considered an unavoidable limitation of recanalization treatment in patients mainly with single vessel disease and preserved left ventricular function, a condition where PCI never showed prognostic benefit. This note of caution is particularly needed after publication of the FUTURE trial (48), a multicenter French registry trying to replicate the FAME trial (49) results with FFR guided revascularization in multivessel disease patients with nearly equal numbers of stable coronary disease or ACS (46%). This French trial was stopped prematurely (after 836 patients, instead of the 1728 scheduled patients) because a significantly higher mortality was observed in the FFR group (3.9% vs. 1.9%,  $P=0.02$ ).

### OCT for stent optimization

The DOCTORS trial (50) (Does Optical Coherence Tomography Optimize Results of Stenting) is the first randomized study comparing OCT and angiographic guidance of coronary stent implantation. The trial was conducted in 240 NSTEMI patients using as end-point the final post-procedural FFR. The value of FFR was higher when OCT was used pre and post-PCI than in the angiography only group ( $0.94 \pm 0.04$  vs.  $0.92 \pm 0.05$ ,  $P=0.005$ ). Post-dilatation was used more frequently in the OCT group (43.0% vs. 12.5%,  $P<0.0001$ ), resulting in a lower residual diameter stenosis ( $7.0 \pm 4.3\%$  vs.  $8.7 \pm 6.3\%$ ,  $P=0.01$ ). Adverse events were similar in two groups. ILUMIEN II (51), an observational study of OCT in patients undergoing PCI, is a recent post hoc ana-

lysis of two studies: ILUMIEN, where stent expansion was guided by OCT in 354 patients, and ADAPT-DES, where IVUS guided stent implantation was used in 586 patients. Stent expansion was similar in the two studies (72.8 vs. 70.6% of the average reference area, respectively,  $P=0.29$ ). The randomized trial ILUMIEN III (52) compared IVUS, OCT and angiographic guidance in 450 patients, showing non-inferiority of the minimal in-stent lumen area obtained with OCT ( $5.79 \text{ mm}^2$  IQR 4.54–7.34 in the OCT group,  $5.89 \text{ mm}^2$  IQR 4.67–7.80 in the IVUS group, and  $5.49 \text{ mm}^2$  IQR 4.39–6.59 in the angiography group) using an imaging end-point based on the reference external elastic membrane, visible also with OCT in >80% of cases. Major malapposition and dissection were more frequent in the IVUS guided group when compared with the OCT group (21% vs. 11%,  $P=0.02$  for malapposition; 26% vs. 14%,  $P=0.009$  for dissection). In the Japanese OPINION trial (53), 800 patients were randomized to IVUS or OCT-guided PCI, showing no differences in the primary endpoint of target vessel failure, including cardiac death, MI caused by target vessel, clinically driven target vessel revascularization after angiographic control at 12 months ( $P=0.833$ ). In the OPINION subanalysis, 100 patients were analysed with OCT ( $n=50$ ) and IVUS ( $n=50$ ) after 8 months, showing greater stent expansion in the IVUS group, approaching statistical significance for mean in-stent lumen area ( $6.56 \text{ mm}^2$  in OCT vs.  $7.51 \text{ mm}^2$  in IVUS,  $P=0.054$ ). This difference in favour of IVUS came at the cost of a higher frequency of dissection ( $P=0.039$  for proximal reference). The numerically lo-



wer strut malapposition in the OCT group did not lead to an increased coverage at the follow-up study after 9 months which showed 4.67% uncovered struts in the IVUS group vs. 6.97% in the OCT group ( $P=0.039$ ).

### OCT to prevent stent thrombosis

OCT, providing high resolution images, can improve the knowledge of the pathophysiology of stent thrombosis. In the French PESTO registry (54) (Morphological Parameters Explaining Stent Thrombosis assessed by OCT), 120 patients with stent thrombosis (75% very late, 6% late, 15% sub-acute, 4% acute) within BMS, DES or bioabsorbable scaffolds were analysed. In 97% of cases an underlying abnormality was found by OCT analysis: malapposition (34%), neoatherosclerotic lesions (22%), (both mainly in late and very late thrombosis), major stent underexpansion (11%), coronary evagination (8%), isolated uncovered struts (8%), edge related-disease progression (8%) and neointimal hyperplasia (4%). In another multicenter European registry (55), 58 patients with very late stent thrombosis with DES were analysed by OCT, conforming that multiple mechanisms cause very late thrombosis. Malapposition (34.5%) and neoatherosclerosis (27.6%), were more frequent than uncovered struts (12.1%) and stent underexpansion (6.9%)

### Adjunctive pharmacologic therapy

#### Prasugrel vs. ticagrelor

The PRAGUE-18 study (56) is the first multicenter randomized study comparing prasugrel and ticagrelor in acute MI undergoing primary PCI. Approximately 1230 out of the expected 2600 patients were randomized at the time the study was prematurely interrupted for futility because the primary end-point (composite of death, re-infarction, urgent TLR, stroke, serious bleeding requiring transfusion or prolonging hospitalization beyond 7 days) was equal in the two groups (4.0% prasugrel vs. 4.1% ticagrelor,  $P=0.939$ ). The premature interruption of the trial and the high frequency of treatment switching, moving to clopidogrel after 7 days, makes this trial unable to provide a credible definitive comparison between ticagrelor and prasugrel.

#### Onset of action of P2Y<sub>12</sub> inhibition

The use of morphine in ACS patients can reduce chest pain but can also delay the onset of action of P2Y<sub>12</sub>-receptor inhibitors. In the IMPRESSION trial (57), 74 MI patients were randomized to receive 5 mg of intravenous morphine or placebo followed by ticagrelor 180 mg. Pharmacokinetic and pharmacodynamic parameters confirmed that morphine reduced total exposure to ticagrelor, showing a concomitant delay in maximal plasma concentration of ticagrelor (4 h in morphine group vs. 2 h in the control group,  $P<0.004$ ). In ACS, a rapid effect of P2Y<sub>12</sub> inhibitors is very important but also in

elective PCI a sufficient platelet inhibition at the start of PCI has to be obtained to decrease MI and stent thrombosis. The EXCELSIOR-LOAD trial (58) (Impact of Extent of Clopidogrel-Induced Platelet Inhibition during Elective Stent Implantation on Clinical Event Rate-Advanced Loading Strategies) showed suboptimal still elevated platelet reactivity (defined as  $>468$  AU/min in aggregometry tests) in 55% of 100 patients loaded with clopidogrel 600 mg, in 37% of 100 patients receiving prasugrel 30 mg, and 33% of 100 patients receiving prasugrel 60 mg ( $P<0.01$ ). After two hours the platelet reactivity was not significantly different in the three groups with similar 30 day incidence of bleeding events. In patients not pretreated or not optimally reacting to oral P2Y<sub>12</sub> inhibitors, cangrelor plays an important role. A recent subanalysis of the CHAMPION PHOENIX trial (59) confirmed that intravenous cangrelor was more effective than clopidogrel to reduce periprocedural MI at 48 h (3.8% in cangrelor patients vs. 4.7% clopidogrel patients), regardless of MI definition. Another subanalysis showed a reduction of periprocedural complications in patients undergoing PCI for stable angina or ACS treated with cangrelor in comparison to clopidogrel.

### Duration of antiplatelet therapy

In spite of innovations in stent materials and the consequent shortening of double antiplatelet therapy (DAPT), some patients still remain at high risk for ischemic events. Overall a longer than 1 year DAPT offers advantages, as shown in the PEGASUS-TIMI 54 trial (60). The DAPT score (61), including clinical history and angiographic features, is a useful instrument to identify patients with expected benefit of a longer DAPT. Balancing ischemic and bleeding risk it permits personalized tailored DAPT duration. In the OPTIDUAL trial (62) (OPTImal DUAL antiplatelet therapy), 1385 patients were randomly assigned to continuing clopidogrel 75 mg daily after 1 year DAPT (extended-DAPT group) or discontinuing clopidogrel (aspirin group). Due to premature termination of enrolment, no differences were shown in the composite primary end-point of death, MI, stroke, or major bleeding (5.8% in extended-DAPT group and 7.5% in aspirin group,  $P=0.17$ ), mortality rate (2.3% vs. 3.5%, respectively,  $P=0.18$ ) and major bleedings (2.0% in both groups).

#### Triple antithrombotic therapy

Approximately 5–21% of patients undergoing PCI for ACS have concomitant atrial fibrillation and a growing number of atrial fibrillation patients are treated with new oral anticoagulants. The PIONEER-AF PCI (63) trial is an open-label, randomized, controlled, multicenter study exploring two treatment strategies of rivaroxaban and oral vitamin K antagonist in subjects undergo PCI. The study randomized 2100 patients to receive rivaro-

xaban 15 mg once daily plus clopidogrel 75 mg for 12 months or rivaroxaban 2.5 mg twice daily plus DAPT or dose-adjusted VKA once daily plus DAPT. The primary end-point (a composite of TIMI major and minor bleeding requiring medical attention) showed a significant advantage of both rivaroxaban groups against the VKA group (16.8% first group, 18% second group, 26.7% in VKA group,  $P < 0.01$ ). All cause death or hospitalization were reduced in the rivaroxaban arms (first group, NNT 15, second group NNT = 10).

### Other drugs

In the GLAGOV trial (64) (Global Assessment of Plaque Regression With a PCSK9 Antibody as Measured by Intravascular Ultrasound), Evolocumab was tested against statin therapy in patients with coronary artery disease for 76 weeks. In this multicenter placebo-controlled trial, 484 patients treated with evolocumab showed not only a lowering of LDL-C mean values compared with placebo group (36.6 vs. 93.0 mg/dL, respectively,  $P < 0.01$ ) but also a significant reduction of percent atheroma volume in IVUS analysis (decrease of 0.95% vs. increase of 0.05%, respectively), and a reduction of total atheroma volume (from 5.8 mm<sup>3</sup> with evolocumab to 0.9 mm<sup>3</sup> with placebo,  $P < 0.01$ ). This raised expectations of clinically significant results in the FOURIER trial, with publication expected at ACC in March 2017.

### Conclusions

The main clinically relevant messages from the year 2016 in coronary interventions can be summarized as follows.

Follow-up up to 10 years shows that surgical revascularization is advantageous in coronary patients with impaired left ventricular function when compared with optimal medical therapy alone, prompting repeated late analyses of all other trials showing equivalence of optimal medical therapy and revascularization. New randomized data support the bold decision of the 2014 European Society of Cardiology Myocardial Revascularization Guidelines to give an equal recommendation class to PCI and CABG for left main disease. This year was definitely not the year of the universal switch from metallic to bioabsorbable drug eluting stents, in spite of reassuring data from large randomized trials with concerns raised by conflicting data from large randomized trials. Current generation scaffolds are early devices and main need further iterative improvements before being able to compete with currently available high performance DES.

The unpredictable absorption time and onset of action also with the newer antiplatelet oral agents offers a window of opportunity for novel intravenous antiplatelet agents, while a longer than 1 year DAPT should be considered with a tailored approach. A triple antiplate-

let/antithrombotic therapy remains an unresolved question, with low dose new oral anticoagulants proposed as alternative components of treatment in this setting. New injectable cholesterol lowering drugs for the first time showed a significant reduction of plaque volume that mirrors the greater efficacy in LDL cholesterol reduction.

### Conflict of interest

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