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The year in cardiology 2017: coronary interventions

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Preamble

The first balloon coronary angioplasty was performed in Zurich by *Andreas Grüntzig* in 1977. The patient, a 38-year-old man with severe angina and a tight stenosis on the left anterior descending artery, is still alive, is doing well, and he celebrated the 40 year anniversary of his percutaneous coronary interventions (PCI) in 2017 *(Figure 1)*. During the last decades, PCI techniques have undergone major improvements with the first real game changer being the introduction of bare metal stents, which made PCI safer and improved longer-term outcomes. Later on, drug-eluting stents (DESs) were introduced, which resulted in a major reduction in restenosis and also – with the newer generation DES – a low rate of stent thrombosis. Further, the introduction of intracoronary pressure measurements for assessment of severity of coronary stenosis [fractional flow reserve (FFR) and instantaneous wave-free ratio (iFR)] and intracoronary imaging [intravascular ultrasound (IVUS) and optical coherence tomography (OCT)] for lesion assessment has refined lesion and procedure assessment. Improved outcomes were also fostered by development of better and safer adjunctive antithrombotic drugs and secondary prevention, optimizing drug-device synergy. Still, 40 years later the research in the coronary interventional field is very intense, and we aim here to summarize major developments in PCI published in 2017.

FIGURE 1. The first patient (left) to receive balloon angioplasty by *Andreas Grüntzig* in 1977 standing next to the President of EAPCI, *Professor Michael Haude* (middle), and *Professor Bernhard Meier* (right)

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Myocardial revascularization

Percutaneous coronary intervention technique

The SYNTAX (Synergy between PCI with Taxus and Cardiac Surgery) II study investigated the impact of a contemporary PCI strategy on clinical outcomes of 454 patients with three-vessel disease (1). Characteristics of the SYNTAX II strategy that captures all components of today's 'best of PCI practice' are summarized in *Figure 2*. Following this approach systematically, the authors demonstrated major adverse cardiac and cerebrovascular events (MACCE) at 1 year to be much improved with respect to a matched historical PCI cohort from the

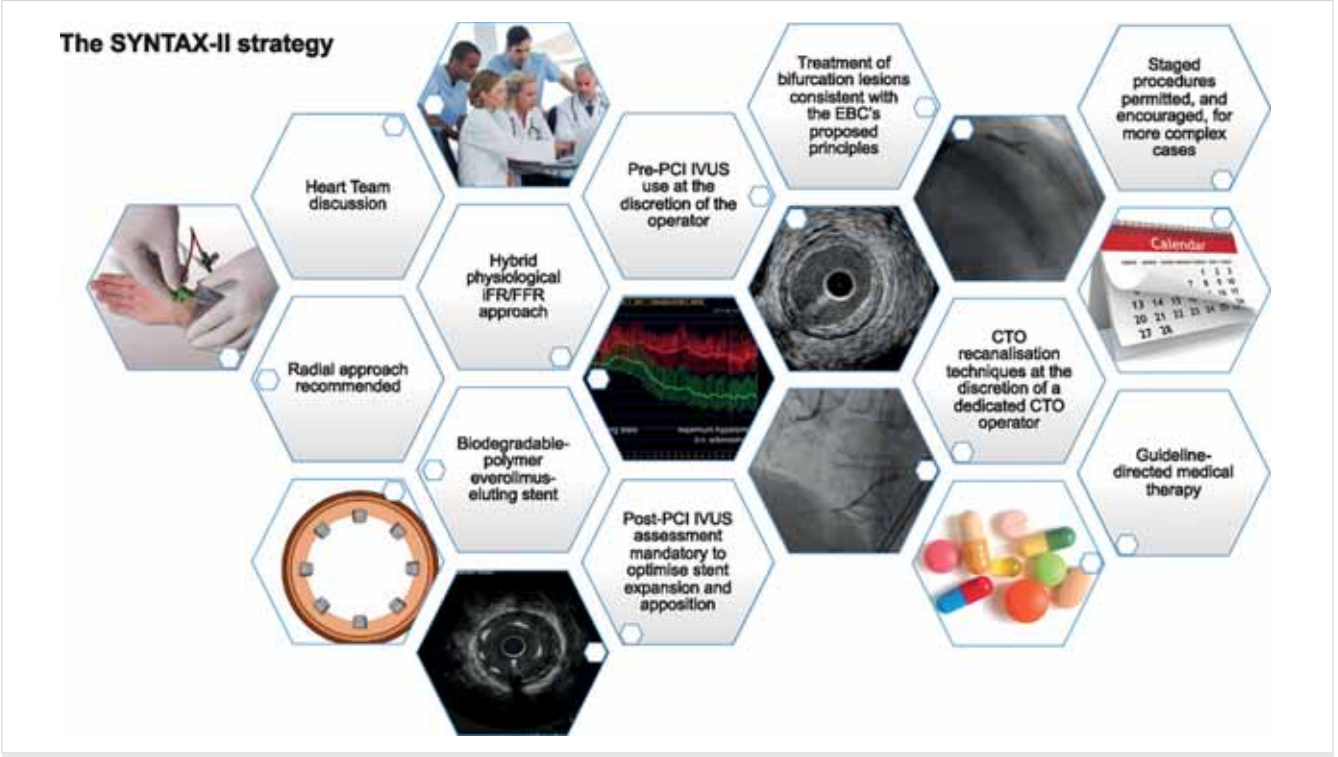

FIGURE 2. Combined advances in percutaneous coronary intervention performance defining the 'Best of PCI Practice' applied in the SYNTAX-II study, as described by Escaned et al (1) reproduced with permission from the European Heart Journal

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SYNTAX I trial (10.6% vs. 17.4%; P=0.006). The better result of the contemporary PCI strategy compared with the procedural technique followed at the time of the SYNTAX I trial was driven by a lower risk of myocardial infarction (MI) and revascularization, with a parallel reduction in stent thrombosis. Overall, the SYNTAX II study suggests that the combination of best practice components in PCI technique portends improved patient outcomes beyond what can be achieved by introducing one single new element. Because these results outperform PCI results obtained in the earlier SYNTAX I trial, the hypothesis was generated that a new randomized study of modern best PCI practice in patients with three-vessel disease might show non-inferiority vs. coronary artery bypass grafting (CABG) (1).

Glimpsing to the future, the feasibility and technical success of robotically-assisted PCI for complex coronary lesions were investigated in 334 procedures from 315 patients included in the Complex Robotically Assisted Percutaneous Coronary Intervention (CORA-PCI) study (2). In 108 procedures of robotically-assisted PCI, technical success was 91.7% and clinical success was 99.1%. A propensity-matched analysis of 82 pairs showed that the procedures were longer in patients undergoing robotically-assisted PCI compared with patients undergoing standard PCI, but clinical success rates were similar (2). Robotically-assisted PCI might find its niche sooner than expected, boosted by the opportunity to further reduce radiation burden to the operator and team.

Contrast-induced nephropathy

The impact of different strategies for prevention of contrast-induced nephropathy is still a matter of debate. The effect of intravenous saline for patients undergoing an elective procedure requiring iodinated contrast material administration was tested in the single-centre, open-label A MAastricht Contrast-Induced Nephropathy Guideline (AMACING) trial, where 660 consecutive subjects with an estimated glomerular filtration rate of 30–59 mL per min/1.73 m^2 were randomized to receive intravenous isotonic saline or no prophylaxis (3). Contrast-induced nephropathy occurred in 2.6% of non-hydrated patients and in 2.7% of hydrated patients, meeting the criteria for non-inferiority of no prophylaxis. Notably, intravenous hydration was associated with higher costs and rates of clinical sequelae, including symptomatic heart failure and arrhythmias.

A network meta-analysis of 28,240 patients undergoing PCI from 124 randomized trials compared 10 different strategies for preventing contrast-induced nephropathy (4). Statin administration was associated with a marked and consistent reduction in the risk of contrast-induced nephropathy compared with saline, while the evidence for the benefit of other treatment strategies (i.e. xanthine, N-acetylcysteine, sodium bicarbonate, ischaemic

preconditioning, and natriuretic peptide) was less robust by sensitivity analyses (4).

Percutaneous coronary intervention vs. coronary artery bypass grafting for left main disease

After publication of the Evaluation of XIENCE vs. Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) and Nordic-Baltic-British left main revascularisation study (NOBLE) trials in 2016, a plethora of updated meta-analyses of PCI vs. CABG for unprotected left main coronary artery disease (CAD) has been published this year. Taking a cautious approach to these mid-term data, it seems that CABG may protect against further revascularization and that there is no significant difference with regard to all-cause mortality. A patient-centred strategy, based on a heart team conference decision taking patient preference and relevant comorbidities into consideration, seems to be the way forward based on the currently available data.

Treatment of chronic total occlusion

Three trials of PCI for chronic total occlusion (CTO) plus guideline-directed medical therapy vs. guideline-directed medical therapy alone (DECISION-CTO, EuroCTO, REVASC) have been presented this year at major interventional cardiology meetings, but are currently unpublished. In view of their premature termination or small sample size, these trials do not address conclusively the debate on the benefit of CTO revascularization with PCI. Although there was no difference in mortality and MI, this may have been due to excessive cross-over rates and concomitant treatment of other non-occlusive lesions. Moreover, the only trial with a quality-of-life endpoint (EuroCTO) reached a difference in favour of PCI in CTO lesions, which may be all you can expect with short-term follow-up in patients with stable angina and primarily non-LAD lesions.

Percutaneous coronary intervention in bifurcations

Systematic two stent techniques are not necessary for the majority of bifurcation lesions. However, bifurcations with large side branches and significant ostial disease length are typically treated with a two-stent technique upfront. The validity of this concept has been challenged by the EBC (European Bifurcation Club) trial, which randomized 200 patients with large caliber true bifurcation lesions and significant ostial disease length (≥ 5 mm) to either a provisional T-stent strategy (resulting in the use of two stents in 16% of cases) or a dual stent culotte technique (5). The composite of all-cause death, MI, and target vessel revascularization at 1 year follow-up did not differ significantly between groups, while procedure time, radiation dose and cost considerations favoured the simpler strategy (5).

In contrast with these results, the Double Kissing and Double Crush vs. Provisional T Stenting Technique for the Treatment of Unprotected Distal Left Main True Bifurcation Lesions (DK-CRUSH) V trial, a study of a planned double kissing crush technique vs. provisional stenting for left main PCI of true bifurcation lesions (N = 482) found a significant reduction in target lesion failure (TLF) at 12 months with the two-stent strategy, driven by lower rates of target vessel MI with parallel reduction in stent thrombosis (6). Notably, the double kissing crush technique also showed favourable long-term outcomes compared with the culotte technique in left main PCI (7).

Five year outcomes of the double kissing crush technique from the DKCRUSH-II trial have also become available (8). In this study, a total of 370 patients with bifurcation lesions were randomly assigned to the double kissing crush or provisional stenting strategies (resulting in 28.6% of cases with double stent use). At 5 years, MACE occurred in 23.8% of patients in the provisional group and 15.7% of patients in the double kissing crush group, trending towards statistical significance (P = 0.051).

Despite the above data, the debate on how to best approach bifurcations with large diseased side branches or left main bifurcation stenosis continues. In such lesions the DKCRUSH may be considered if an upfront two-stent technique is chosen. However, many operators favour a single-stent strategy, with use of provisional culotte or T-stenting strategies, in the majority of cases.

In-stent restenosis

Strategies for improving PCI for in-stent restenosis continue to be the object of ongoing investigation. In the Intracoronary Stenting and Angiographic Results: Optimizing Treatment of Drug-Eluting Stent In-Stent Restenosis (ISAR-DESIRE) 4 trial, modification of in-stent restenosis neointima with scoring balloon pre-dilatation before drug-coated balloon application proved significantly better than a drug-coated balloon standard therapy only with respect to percentage diameter stenosis and angiographic restenosis at 6- to 8-month follow-up angiography (9).

Percutaneous coronary intervention for acute coronary syndromes

Thrombectomy for ST-segment elevation myocardial infarction

A pooled analysis of individual patient data from three large randomized trials [Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction (TAPAS), Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE), and Trial of Routine Aspiration Thrombectomy With PCI vs. PCI Alone in Patients With STEMI (TOTAL)] provi-

ded novel insights about thrombus aspiration for ST-elevation myocardial infarction (STEMI) (10). By including 18,306 patients, the study did not show a significant reduction in cardiovascular death when thrombus aspiration was compared with standard therapy. There were also no differences between thrombus aspiration and no thrombus aspiration with respect to stroke or transient ischaemic attack, recurrent MI, stent thrombosis, heart failure, or target vessel revascularization (10). Although routine use of mechanical thrombus aspiration is no longer recommended, prior safety concerns regarding the risk of stroke could not be confirmed. Because a trend towards reduced cardiovascular death and increased stroke or transient ischaemic attack was found in the subgroup of patients with high thrombus burden, future studies may want to investigate improved thrombus aspiration technologies in this high-risk subgroup.

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

Management of non-infarct-related coronary arteries after primary PCI for STEMI remains controversial. In the Compare-Acute trial, 885 patients with STEMI and multivessel disease (MVD) who underwent primary PCI were randomized in a 1:2 fashion to complete revascularization of non-infarct-related coronary arteries guided by FFR or no revascularization of non-infarct-related coronary arteries (11). There was a significant reduction in MACCE at 1 year with FFR-guided complete revascularization (8% vs. 21%; P < 0.001). The benefit was mostly driven by a reduced risk of revascularization. A potential drawback is the use of a control group that, in opposition to ESC guidelines (12), was not offered ischaemia-guided full revascularization. Meta-analyses published so far on the topic do not incorporate the results of this study. In one of them focusing on the issue of timing for PCI of non-culprit artery lesions, which encompassed a total of 10 trials with 2285 patients, the reduction in the risk of cardiovascular events was observed irrespective of the timing of non-infarct-related coronary artery revascularization (13). Moreover, the iFR in ST-segment Elevation Myocardial Infarction (iSTEMI) trial suggested that physiological disarrangements in STEMI patients affect functional assessment of non-culprit lesions for at least 5 days while re-evaluation more than 2 weeks after STEMI may yield a physiological assessment comparable to stable conditions *(Thim et al.)* (14). Future studies will assess whether full immediate revascularization or full staged revascularization are the best treatment strategy.

In the setting of cardiogenic shock, the efficacy and safety of treating non-infarct-related coronary arteries in the context of primary PCI has been a matter of debate. In the Culprit Lesion Only PCI vs. Multivessel PCI in Cardiogenic Shock (CULPRIT-SHOCK) trial (N = 706), the 30-day risk of a composite of death or severe renal failure leading to renal-replacement therapy was lower in patients who underwent initial PCI of the culprit lesion only compared with those who underwent immediate multivessel PCI (15).

New clinical practice guidelines for ST-segment elevation myocardial infarction

New guidelines have been released by the European Society of Cardiology in 2017 on the management of patients with STEMI (12). The document incorporates some notable changes in recommendations compared with the previous version published 5 years earlier. From a technical standpoint, recommendation grades for radial access and DES use in primary PCI were upgraded from IIa to I and routine thrombus aspiration was downgraded from IIa to III. Complete revascularization for STEMI patients with MVD was upgraded from III to IIa and routine deferred stenting of the culprit lesion is not recommended (class III). However, the optimal timing (during the procedure, during index hospitalization, staged) of complete revascularization remains to be determined. Grade IIa recommendation was also applied for complete revascularization during the index procedure in STEMI patients with MVD who present with cardiogenic shock. Based on the results of the CULPRIT-SHOCK trial, providing compelling evidence against immediate multivessel PCI in this setting, this recommendation can no longer be supported. On the adjuvant pharmacology side, intraprocedural bivalirudin was downgraded from class I to IIa and enoxaparin was upgraded from IIb to IIa. Cangrelor is now added as IIb for patients who are $P2Y_{12}$-inhibitors-naïve, and ticagrelor is proposed up to 36 months for patients at high ischaemic risk (IIb).

Devices

Drug-eluting stents

Several randomized controlled trials of DES vs. DES reported longer-term follow-up in the past year. These follow-up studies are summarized in *Table 1* (16–20). The overall picture from these comparisons based on non-inferiority trials suggests that the 1 year and long-term outcomes with newer-generation DES is very good without notable differences between brands.

In a DES vs. DES comparison with 1 year follow-up available, the sirolimus-eluting, thin-strut biodegradable-polymer Orsiro stent was evaluated in the BIOFLOW V study (N = 1334) and compared with the durable-polymer Xience stent. Six percent of patients in the Orsiro group and 10% of patients in the Xience group met the 12-month primary endpoint of TLF (P = 0.0399) (21). It is noteworthy that the Xience stent in the BIOFLOW V had higher TLF rate in selected lower-risk patients at 12-month follow-up than in an ‘all-comers’ population at 2 year follow-up in the previous SORT OUT IV trial (5%) (22). The difference in TLF was primarily driven by a difference in target-vessel MI (4.7% vs. 8.3%), which

TABLE 1. Long-term (≥2 years) follow-up of randomized comparisons of drug-eluting stents published in 2017

Study acronym	Study DES	Comparator DES	No of patients	Randomization	Follow-up (years)	End-point	Events	P-value
SORT OUT V (18)	Nobori	Cypher	2468	1:1	5	MACE	14.8% vs. 15.8%	0.53
COMPARE 2 (16)	Nobori	Xience	2707	2:1	5	MACE	17.3% vs. 15.6%	0.26
SORT OUT VI (20)	Resolute	Biomatrix	2999	1:1	3	MACE	8.6% vs. 9.6%	0.36
DUTCH PEERS (17)	Resolute	Promus Element	1811	1:1	3	MACE	11.7% vs. 11.4%	0.77
SORT OUT VII (19)	Orsiro	Nobori	2225	1:1	2	TLFa	6.7% vs. 7.0%	0.71

SORT OUT, Scandinavian Organization for Randomized Trials with clinical OUTcome; DES, drug-eluting stent; MACE, major adverse cardiac events; COMPARE, abluminal biodegradable polymer biolimus-eluting stent vs. durable polymer everolimus-eluting stent; DUTCH PEERS, DUrable Polymer-Based STent CHallenge of Promus ElemEnt vs. ReSolute Integrity; TLF, target lesion failure. aMACE not reported.

was not explained by differences in definite stent thrombosis (0.5% vs. 0.7%) (21).

The SENIOR trial randomized elderly patients undergoing PCI to DES or bare metal stent (BMS) with use of a short duration of dual antiplatelet therapy [DAPT for 1 month in elective patients, 6 months in patients with acute coronary syndromes (ACS)]. The study found a significant reduction in the composite endpoint including all-cause mortality, MI, stroke, and ischaemia-driven target lesion revascularization in the DES group (23). The incidence of bleeding complications was similar (5%) for the DES and BMS groups. The conclusion is that BMS should no longer be preferred to new generation DES when high bleeding risk is of concern and shortened duration of DAPT is desired.

Polymer-free drug-coated stents

The Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug-Coated Stent vs. the Gazelle Bare-Metal Stent in Patients at High Bleeding Risk (LEADERS-FREE) study compared the polymer-free biolimus-eluting Biofreedom stent with a BMS in a cohort (N = 2466) at high risk of bleeding. In a subgroup analysis of 659 ACS patients, treatment with the BioFreedom stent remained more effective (clinically driven target-lesion revascularization 3.9 vs. 9.0%, P = 0.009) and safer (cumulative incidence of cardiac death, MI, or definite or probable stent thrombosis 9.3 vs. 18.5%, P = 0.001), driven by significantly lower rates of cardiac mortality (3.4 vs. 6.9%, P = 0.049) and MI (6.9 vs. 13.8%, P = 0.005) (24). As for the SENIOR trial, there was no difference in bleeding complications for the DES and BMS groups.

These results confirm the clinical utility of polymer-free drug-coated stent for patients at high bleeding risk and a direct comparison with current generation DES would be of great interest.

Bioresorbable scaffolds

ABSORB

The bioresorbable scaffolds, in particular the ABSORB, have received much attention as a potential new major step in coronary intervention following the footsteps of balloon angioplasty, BMS and DES implantation. Data emerged, however, that the first-generation ABSORB scaffold is associated with a higher risk of device-induced adverse end points.

The AIDA trial is the largest ABSORB vs. Xience trial published so far (25). AIDA randomized 1845 patients 1:1 in the context of routine clinical practice. The primary endpoint was target-vessel failure (a composite of cardiac death, target-vessel MI, or target-vessel revascularization). The study was stopped prematurely by the Data Safety Monitoring Committee at a median follow-up of 707 days. Target-vessel failure at 2 years occurred in 11.7% of patients in the ABSORB group and in 10.7% of patients in the Xience group [hazard ratio (HR) 1.12; 95% confidence interval (CI) 0.85–1.48; P = 0.43]. Definite or probable device thrombosis occurred in 3.5% of patients in the ABSORB group and 0.9% in the Xience group (HR 3.87; 95% CI 1.78–8.42; P < 0.001) (25).

In 2017, 3 year outcomes of the ABSORB JAPAN, ABSORB CHINA and ABSORB III and 4 year outcomes of the ABSORB II trial became available. An updated patient-level meta-analysis of the 4 ABSORB trials (N = 3389) comparing clinical outcomes of patients treated with ABSORB and Xience with at least 36 months follow-up documented higher 3 year rates of TLF (11.7% vs. 8.1%, P = 0.006), driven by greater target vessel MI and ischaemia-driven TLR, with device thrombosis also shown to be higher with the ABSORB scaffold. This difference was partly explained by a higher rate of very late stent thrombosis (26).

As of September 14, 2017 the device manufacturer called a worldwide halt to sales of ABSORB. A Task Force of the European Society of Cardiology and European Association of Percutaneous Cardiovascular Interventions provided a report on recommendations for the non-clinical and clinical evaluation of bioresorbable scaffolds and stated that, at present, these devices should not be preferred to conventional DES in clinical practice (27). The Task Force recommends that new bioresorbable scaffold devices should undergo systematic non-clinical testing according to standardized criteria prior to evaluation in clinical studies.

MAGMARIS

As depicted in *Figure 3*, there are several emerging alternatives to the ABSORB. One to these is the second-generation Magmaris, which consists of a magnesium scaffold backbone covered by a sirolimus-eluting bioresobable polylactic acid polymer. The first-in-man BIOSOLVE-II trial enrolled 123 patients with up to two de novo lesions. Quantitative coronary angiography metrics remained stable from 6 to 12 months. Target lesion failure occurred in four (3.4%) patients, consisting of one death of unknown cause, one target-vessel MI and two clinically driven TLR. No additional event occurred beyond the 6-month follow-up. During the entire follow-up of 12 months, none of the patients experienced a definite or probable scaffold thrombosis (28). At 2 year follow-up, TLF was 5.9% due to 2 deaths, 1 MI, and 4 TLR (29). Controlled clinical evaluation for selected indications is continuing but no randomized comparison to DES is available thus far (30).

Functional and imaging guidance

Fractional flow reserve or instantaneous wave-free ratio to guide coronary intervention

FFR has been documented as a valuable tool to guide coronary intervention. The adenosine-free index iFR has

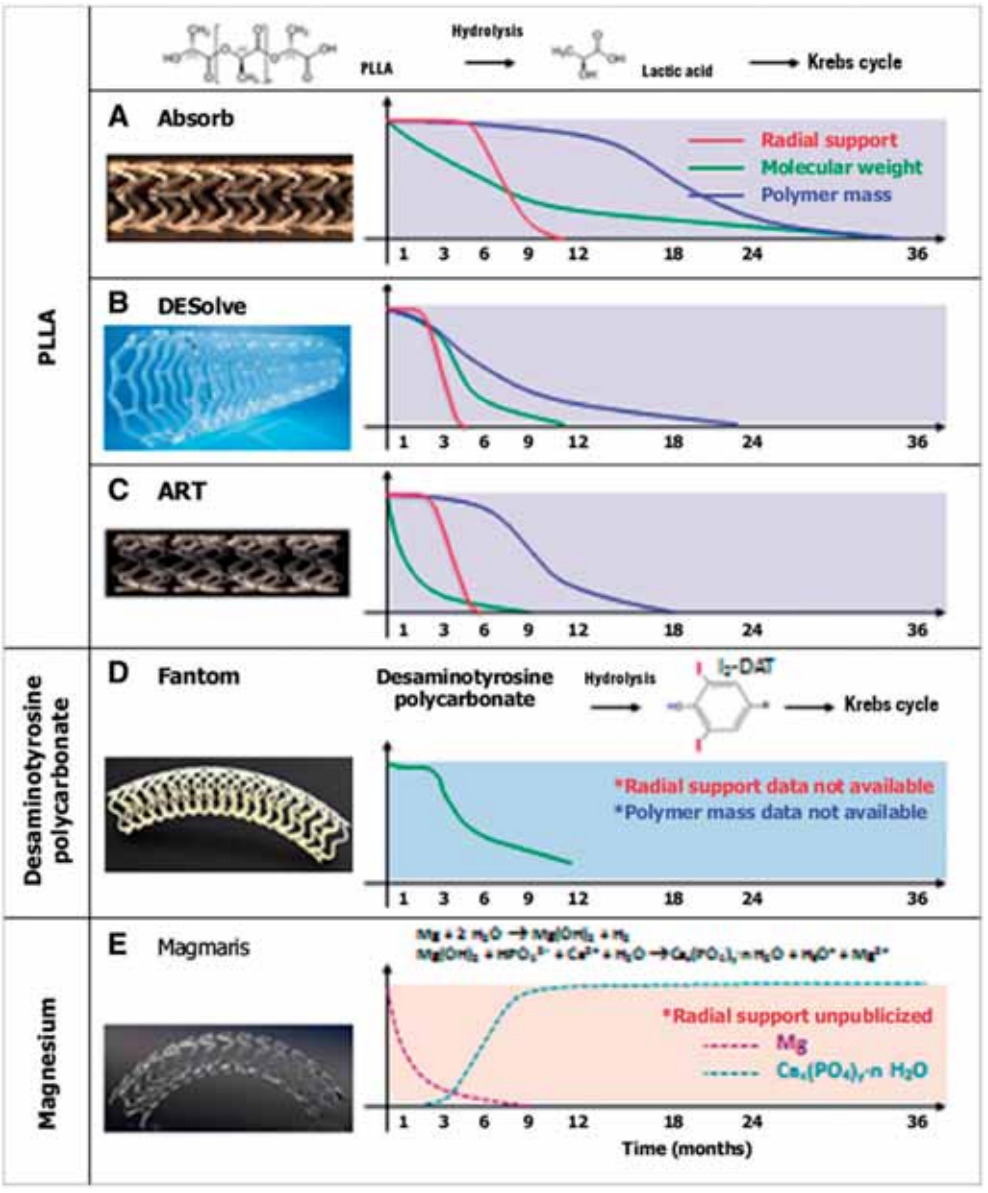

FIGURE 3. Principal degradation characteristics of CE-marked bioresorbable scaffolds. For each device data are shown, where available, for radial support and molecular weight and mass of the polymer over time. For the magnesium scaffold, the content of magnesium and calcium phosphate (a conversion product) over time is shown. PLLA, poly-L-lactic acid. Reproduced after Byrne et al (27) with permission from the European Heart Journal

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emerged as a potential alternative to FFR. However, as documented in comparative studies, iFR and FFR have classification disagreement in up to one of five evaluated lesions (31). Until 2017, it remained unclear how this would affect clinical outcomes in prospective randomized studies using iFR vs. FFR to guide intervention. The Functional Lesion Assessment of Intermediate Stenosis to Guide Revascularisation (DEFINE-FLAIR) (32) (N = 2492) and Instantaneous Wave-free Ratio vs. Fractional Flow Reserve in Patients with Stable Angina Pectoris or Acute Coronary Syndrome (iFR-Swedeheart) (33) (N = 2038) clinical trials both examined if iFR was non-inferior to FFR for PCI guidance. The primary endpoint in both studies was a composite of death from any cause, non-fatal MI, or unplanned revascularization at 1 year follow-up. In the DEFINE-FLAIR study, the primary endpoint occurred in 6.8% in the iFR group and in 7.0% in the FFR group (P < 0.001 for non-inferiority) (32). In the iFR-Swedeheart study, the primary endpoint occurred in 6.7% in the iFR group as compared with 6.1% in the FFR group (P = 0.007 for non-inferiority). Moreover, iFR was associated with shorter procedural time and less procedural discomfort (33). Both approaches are now validated and future studies will analyse causes for discrepancy. At 1 year follow-up though, this does not seem to matter much and both modalities can be used for PCI guidance.

Intravascular ultrasound and optical coherence tomography to guide percutaneous coronary intervention

Two randomized clinical trials compared imaging techniques for PCI guidance. In the Optical frequency domain imaging vs. intravascular ultrasound in percutaneous coronary intervention (OPINION) trial (N = 829), OCT-guided PCI was non-inferior to IVUS-guided PCI with respect to the composite of cardiac death, target-vessel related MI, and ischaemia-driven target vessel revascularization at 1 year (34). In the Optical coherence tomography compared with intravascular ultrasound and with angiography to guide coronary stent implantation (ILUMIEN III) trial (N = 450), OCT-guided PCI using a specific stent optimisation strategy resulted in similar minimum stent area compared with IVUS-guided PCI (35). These two trials are incorporated in an updated network meta-analysis suggesting that the use of intravascular imaging techniques for PCI guidance reduces the risk of cardiovascular death and adverse events (36).

Adjunctive pharmacology

Risk stratification for bleeding

The PRECISE-DAPT score (age, creatinine clearance, haemoglobin, white-blood-cell count, and previous spontaneous bleeding) was derived from 14,963 patients treated with different duration of DAPT (mainly aspirin and clopidogrel) after coronary stenting and showed a c-index for out-of-hospital TIMI major or minor bleeding of 0.73 (95% CI 0.61–0.85) (37). A longer DAPT duration significantly increased bleeding in patients at high risk (score ≥ 25), but did not in those with lower bleeding risk profiles, and exerted a significant ischaemic benefit only in this latter group. As stated in the new ESC/EACTS Consensus document on DAPT, the use of risk scores such as PRECISE-DAPT designed to evaluate the benefits and risks of different DAPT durations 'may be considered' to support decision making (38).

Anticoagulation for percutaneous coronary intervention

According to the 2017 ESC STEMI Guidelines, routine use of bivalirudin during primary PCI is a class IIa recommendation (12). After release of these guidelines, a multicentre, randomized, registry-based trial was published, named Bivalirudin vs. Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated according to Recommended Therapies Registry Trial (VALIDATE-SWEDEHEART trial) (39). Patients with either STEMI (N = 3005) or non-STEMI (N = 3001) undergoing PCI and receiving a potent $P2Y_{12}$ inhibitor (ticagrelor, prasugrel, or cangrelor) without the planned use of glycoprotein IIb/IIIa inhibitors were randomly assigned to receive bivalirudin or heparin during PCI, performed predominantly with the use of radial artery access. The primary composite endpoint (death from any cause, MI, or major bleeding during 180 days of follow-up) occurred in 12.3% of the patients in the bivalirudin group and in 12.8% of the patients in the heparin group (HR 0.96; 95% CI 0.83–1.10; P = 0.54). The results were consistent between patients with STEMI and those with non-STEMI and across other major subgroups. There was no difference between groups in MI, major bleeding, definite stent thrombosis or mortality. This study shows overall clinical non-inferiority for use of bivalirudin or heparin during PCI for ACS, along with increased cost with use of bivalirudin. Consistently with these findings, the current use of bivalirudin in Europe is very low.

Dual antiplatelet therapy

Ticagrelor reduces ischaemic events and mortality in ACS patients compared to clopidogrel and is recommended by current guidelines (12). Clinical outcomes in a large real-world post-ACS population was studied in a Swedish prospective cohort study in 45,073 ACS patients who were discharged on ticagrelor (N = 11,954) or clopidogrel (N = 33,119) (40). The ri sk of the primary outcome (composite of all-cause death, re-admission with MI, or stroke) with ticagrelor vs. clopidogrel

was 11.7% vs. 22.3% [adjusted HR 0.85 (95% CI 0.78–0.93)], risk of death 5.8% vs. 12.9% [adjusted HR 0.83 (0.75–0.92)], and risk of MI 6.1% vs. 10.8% [adjusted HR 0.89 (0.78–1.01)] at 24 months. Re-admission for bleeding with ticagrelor vs. clopidogrel was similar. Ticagrelor vs. clopidogrel post-ACS was associated with a lower risk of death, MI, or stroke, as well as death alone. Risk of bleeding was higher with ticagrelor (40). These real-world outcomes are consistent with the results of the landmark Platelet Inhibition and Patient Outcomes (PLATO) trial (41).

Dual antiplatelet therapy and surgery

The present Guidelines recommend postponing elective non-cardiac surgery for 6 months after PCI with DES (42). The surgical risk compared with that in non-stented patients without CAD was investigated in 22,590 patients undergoing DES-PCI in Western Denmark (43). Using Danish registries, 4303 DES-PCI-treated patients undergoing a surgical procedure were compared with a control group of patients without previous CAD undergoing similar surgical procedures (N = 20,232). Surgery in DES-PCI-treated patients was associated with an increased risk of MI [1.6% vs. 0.2%; odds ratio (OR) 4.82; 95% CI 3.25–7.16] and cardiac death (1.0% vs. 0.2%; OR 5.87; 95% CI 3.60–9.58) but not all-cause mortality (3.1% vs. 2.7%; OR 1.12; 95% CI 0.91–1.38). When stratified for time from PCI to surgery, only surgery within the first month was associated with a significant increased risk of events, suggesting that surgery might be undertaken earlier than currently recommended.

Dual antiplatelet therapy duration

Recommendations on duration of DAPT in patients with ACS and after elective stenting have been given in the ESC/EACTS focused update on DAPT (38). Recently the 2 year follow-up report of the Is There a Life for DES After Discontinuation of Clopidogrel (ITALIC) study (N = 2031) confirmed the 1 year results and showed that patients receiving 6-month DAPT after PCI with second-generation DES have similar outcomes to those receiving 24-month DAPT (44).

Another study pooled patient-level data from six randomized controlled trials and investigated the efficacy and safety of long-term (≥12 months) vs. short-term (3 or 6 months) DAPT with aspirin and clopidogrel after PCI (45). Of 9577 patients included in the pooled dataset for whom procedural variables were available, 1680 (17.5%) underwent complex PCI. Overall, 85% of patients received new-generation DES. At a median follow-up time of 392 days, patients who underwent complex PCI had a higher risk of MACE (HR 1.98; 95% CI 1.50–2.60; P < 0.0001). Compared with short-term DAPT, long-term DAPT yielded significant reductions in MACE in the complex PCI group (adjusted HR 0.56; 95% CI 0.35–0.89) vs. the non-complex PCI group (adjusted HR 1.01; 95% CI 0.75–1.35; P-value for interaction = 0.01). The magnitude of the benefit with long-term DAPT was progressively greater per increase in procedural complexity. Long-term DAPT was associated with increased risk for major bleeding, which was similar between groups (45). Results were consistent by per-treatment landmark analysis and further establish procedural complexity as an important parameter to take into account in tailoring upfront duration of DAPT (38).

A large individual patient data pairwise and network meta-analysis comparing short-term (≤6-months) vs. long-term (1 year) DAPT as well as 3-month vs. 6-month vs. 1 year DAPT included 11,473 patients (46). The primary study outcome was the 1 year composite risk of MI or definite/probable stent thrombosis. Six trials including 11,473 randomized patients in which DAPT after DES consisted of aspirin and clopidogrel: 6714 (58.5%) had stable CAD and 4758 (41.5%) presented with ACS, the majority of whom (67.0%) had unstable angina. In ACS patients, ≤6-month DAPT was associated with non-significantly higher 1 year rates of MI or stent thrombosis compared with 1 year DAPT (HR 1.48, 95% CI 0.98–2.22), whereas in stable patients, the rates of MI and stent thrombosis were similar between the two DAPT strategies (HR 0.93, 95% CI 0.65–1.35). By network meta-analysis, 3-month DAPT, but not 6-month DAPT, was associated with higher rates of MI or stent thrombosis in ACS, whereas no significant differences were apparent in stable patients. Short DAPT was associated with lower rates of major bleeding compared with 1 year DAPT, irrespective of clinical presentation. All-cause mortality was not significantly different with short vs. long DAPT in both patients with stable CAD and ACS (46).

The studies mentioned above support the concept that duration of DAPT should be individualized as discussed in detail in the ESC/EACTS DAPT Consensus document (38).

Platelet testing

Current ESC Guidelines do not recommend routine testing of platelet function in patients treated with platelet inhibitors as randomized trials have failed to demonstrate any benefit of testing to adjust antiplatelet therapy (12, 38, 47). In a recent study, 2610 patients with ACS who had been undergoing successful PCI were randomized to standard treatment with prasugrel for 12 months (control group) or a step-down regimen (1 week prasugrel followed by 1 week clopidogrel and platelet function testing-guided maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge; guided de-escalation group). The primary endpoint was net clinical benefit [cardiovascular death, MI, stroke, or bleeding grade 2 or higher according to Bleeding Academic Research Consortium (BARC) criteria] 1 year after randomization, which occurred in 7% of patients in the guided de-escalation group and in 9% in the control group (P-value for non-inferiority = 0.0004;

P-value for superiority = 0.12). Despite early de-escalation, there was no increase in the combined risk of cardiovascular death, MI, or stroke in the de-escalation group (3% vs. 3%; P-value for non-inferiority = 0.0115). Bleeding Academic Research Consortium 2 or higher bleeding events were similar between groups (48). Although costly and time-consuming, early de-escalation of antiplatelet treatment guided by platelet function testing may be an alternative approach in some patients. On a similar subject but with no use of platelet function testing guidance, the TOPIC (timing of platelet inhibition after acute coronary syndrome) trial showed that de-escalation from prasugrel or ticagrelor to clopidogrel after 30 days from the ACS may achieve lower bleeding rates than standard therapy with the more potent P2Y12 inhibitors for 12 months (49).

Triple antithrombotic therapy

Triple therapy with oral anticoagulants plus DAPT is associated with increased bleeding risk, but is still used after PCI for patients with atrial fibrillation. Recent studies have indicated that the duration of triple therapy should be as short as possible and dual-pathway therapy with an anticoagulant and an antiplatelet agent can be considered as an alternative to reduce the risk of bleeding. In the RE-DUAL PCI trial, 2725 patients with atrial fibrillation who had undergone PCI were randomized to triple therapy with warfarin plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and aspirin (for 1–3 months) (triple-therapy group) or dual therapy with dabigatran (110 mg or 150 mg twice daily) plus a P2Y12 inhibitor (clopidogrel or ticagrelor) and no aspirin (110 mg and 150 mg dual-therapy groups) (50). The primary endpoint was a major or clinically relevant non-major bleeding event during follow-up. Ticagrelor, however, increased the risk of bleeding events. The incidence of the primary endpoint was 15.4% in the 110 mg dual-therapy group as compared with 26.9% in the triple-therapy group (HR 0.52; 95% CI 0.42–0.63) and 20.2% in the 150 mg dual-therapy group as compared with 25.7% in the corresponding triple-therapy group (HR 0.72; 95% CI 0.58–0.88). The incidence of the composite efficacy endpoint was 13.7% in the two dual-therapy groups combined as compared with 13.4% in the triple-therapy group (HR 1.04; 95% CI 0.84–1.29) (50). Subgroup analyses of the RE-DUAL PCI study presented at the American Heart Association Meeting in November 2017 confirmed that the benefit of the dabigatran dual therapy vs. warfarin triple therapy was consistent with the main results in both patients with ACS and non-ACS, and among patients receiving ticagrelor instead of clopidogrel.

This study is consistent with the previous Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects with Atrial Fibrillation who Undergo Percutaneous Coronary Intervention (PIONEER-AF) study of rivaroxaban (51) and these studies provides alternatives to full-dose triple therapy in patients with atrial fibrillation undergoing coronary stenting (38).

Conclusions

In 2017, a large number of articles increased our understanding and modified our treatment strategies within the field of interventional cardiology. Newer-generation DESs maintain solid results regarding long-term safety (16–20). Major reductions in bleeding rates were found when triple therapy with warfarin, aspirin, and clopidogrel was reduced to dual therapy with dabigatran and clopidogrel in patients with atrial fibrillation (50). Heparin was effective as bivalirudin in STEMI patients treated with PCI(39). However, no revolutions occurred in 2017, only refinements were made.

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In parallel, important studies on lipid-lowering with PCSK9 inhibitors (52), a cholesteryl ester transfer protein inhibitor (53), therapeutic monoclonal antibody targeting interleukin-1beta anti-inflammatory therapy (54) and addition of very low dose rivaroxaban to aspirin (55) have been shown to improve cardiac outcomes in patient with stable CAD. These developments plus changes in life style are expected to further increase cardiovascular health through optimized drug-device synergy.

Conflict of interest: S.D.K. has received lecture fees from Aspen, AstraZeneca, Bayer, BMS/Pfizer and Boehringer-Ingelheim. M.M. has received lecture fees and consulting honoraria from Novo, Bayer, AstraZeneca, Boehringer-Ingelheim, and institutional grants from Volcano (now Philips), Boston Scientific, and Biosensors. D.C. has received lecture fees and consulting honoraria from AstraZeneca, Bayer and Abbott Vascular. W.W. is co-founder of Argonauts Partners, an innovation facilitator and reports institutional grants from Abbott, MiCell, MicroPort, Terumo and lecture fees from Abbott, Biotronik and MicroPort.

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