The Year in Cardiology 2013: coronary intervention

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Received 13 November 2013; revised 26 November 2013; accepted 28 November 2013

The year 2013 was rich of new developments in cardiology, and percutaneous coronary intervention (PCI) in particular. This overview article will focus on contributions in the following areas: training for PCI, appropriateness and indications; access site selection, risk scores, peri-procedural myocardial infarction; trial results and long-term follow-up; PCI for specific patient and lesion subsets, including acute coronary syndrome and ST-segment myocardial infarction; prevention of ischemic and reperfusion injury; stent thrombosis and new coronary stents and scaffolds.

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Keywords
- PCI
- Intervention
- Interventional cardiology
- Coronary intervention

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The year 2013 was rich of new developments in cardiology, and percutaneous coronary intervention (PCI) in particular, as summarized in this article.

Training for percutaneous coronary intervention, appropriateness, and indications

Training
Increasingly complex PCI procedures are performed in patients at higher risk with increasing impact of operator’s experience on clinical outcomes. In-hospital and up to 5-year safety outcomes of PCI undertaken either by trainees (working in a structured training environment) or by consultant operators were compared. Patients who have been treated by a consultant (n = 7505) or a trainee (n = 8502) had comparable in-hospital rates of stroke, emergency bypass surgery (CABG), and repeat PCI. The only independent outcome predictor for all-cause mortality was the clinical presentation of the patient himself.1 Use of a virtual catheterization laboratory reality simulator seems to offer a unique opportunity to complement training of young interventionalists by providing learning experience and feedback to the trainee that would otherwise require practice on patients.2

Appropriateness
The appropriateness of indications of PCI has been challenged, particularly in the USA. Whereas only 1.1% of emergency procedures were regarded as inappropriate, up to 10-fold higher rates were reported for non-acute PCI.3 In addition to immediate technical success of PCI, the focus should be placed on long-term patient-oriented outcomes, quality metrics, and implementation of trial-based evidence.4

Indications
Using the hyperaemic pressure-derived fractional flow reserve (FFR), the long-term outcomes of patients undergoing PCI with angiographic guidance only (n = 6268) were compared with PCI with FFR guidance (n = 1090) or deferred PCI (n = 721). At 7 years, major adverse cardiac events (MACE) were 50% in patients with FFR-guided PCI, compared with 57% in patients treated with angiographic guidance (P = 0.016). The defer strategy in patients with preserved FFR was independently associated with reduced rate of myocardial infarction (MI), hazard ratio (HR) 0.46, 95% confidence intervals (CI) 0.26–0.82, P = 0.008.5 The clinical impact of routine incorporation of FFR in real practice was tested in 5097 patients with death, MI, and repeat revascularization at 1 year as endpoints.6 With nearly half the stents implanted, primary endpoint (Figure 1) was significantly lower in patients treated after the routine use of FFR (FFR in 50.7% of all cases) vs. before (FFR in 1.9% of all cases): HR 0.55, CI 0.43–0.70 (P < 0.001). Implementation
of FFR-based PCI strategies in daily practice is associated with improved clinical outcomes in both studies.5,6

Access site selection, risk scores, and peri-procedural myocardial infarction

Access site selection

The long-standing controversy on access site selection has evolved with an increasing worldwide use of the radial instead of the femoral approach, particularly following the presentation of the RIVAL trial.7 The benefit of radial access is to reduce bleeding complications, with some remaining concerns regarding prolonged fluoroscopy time. Radiation exposure, measured by median air kerma, was reduced with the femoral approach only in low volume radial centres, underlying the importance of proper training.8 Another potential advantage of radial access is the performance of PCI as an ambulatory procedure. Previously PCI without stenting was associated with high rates of (sub)acute coronary occlusion, requiring emergency angiography, followed by emergency repeat PCI or even CABG. Today predictability and stability of immediate PCI results allow same-day discharge in selected patients, already proposed by Kiemeneij et al.9 Consecutive patients (n = 200) were discharged on the same day without major bleeding or MACE at 24 h and at 7 days. Minor bleedings were noted in 4% of the patients, 2% were admitted to hospital, and only 1.5% had emergency revisits.10 The increasing use of radial access will provide an opportunity for further medical and economic evaluation of same-day PCI strategies.

Risk scores

Multiple risk scores for the prediction of mortality after PCI have been validated and reviewed in ESC Practice Guideline recommendations.11 Most algorithms have identified the age, gender, cardiovascular risk factors, elevated creatinine, recent MI, and peripheral vascular disease as the strongest predictors of risk. The SYNTAX investigators calculated the 1-year risk for all cause death and MACE using the combination of SYNTAX score, age, ejection fraction, and creatinine clearance. The score provided excellent predictive accuracy12 and further enhanced the 5-year risk stratification for PCI or CABG.13 Based on three angiographic and five clinical variables, this score provides an excellent tool for the heart team discussion in order to determine the optimal treatment strategy for each patient, from a personalized care perspective.

Peri-procedural myocardial infarction

The Third Joint ESC/ACCF/AHA/WHF Task Force14 has issued new consensus definitions of peri-procedural MI (type 4a). The clinical significance of frequently observed peri-procedural elevations of
Specific patient and lesion subsets

Gender-related issues have become a topic of major interest in cardiology and other medical disciplines. A patient-level pooled analysis of 26 randomized trials involving 11,557 women looked at safety and efficiency of bare-metallic stent (BMS) and DES in women. At 3 years, the incidence of death and MI decreased dependent on the stent type from 12.8 to 10.9% and 9.2% comparing BMS to the newer DES generation. At variance with results of prior smaller studies and meta-analyses, of note, a detailed pilot randomized study using optical frequency domain imaging in primary PCI (141 patients) was not able to show differences between cases with and without thrombectomy in relation to minimal lumen area, plaque protrusion, intraluminal defects, complete and incomplete stent apposition. The TASTE study is the largest available randomized trial, nested in the SCAAR and SWEDHEART nationwide registries, and involved 31 sites, all primary PCI centres in Sweden, 1 in Denmark and another in Iceland. The primary endpoint—all cause mortality—at 30 days was not different between 7244 patients randomized to either immediate PCI (n = 3623) or manual thrombus aspiration plus PCI (n = 3621); the HR was 0.94 (CI 0.72–1.22; P = 0.63). The secondary endpoints mortality and re-MI rates at 30 days were 3.9 and 3.3%, respectively (P = 0.23). Secondary endpoints of Re-MI (HR 0.61; CI 0.34–1.07) and stent thrombosis (HR 0.47; CI 0.20–1.02) were not significantly different, with low stent thrombosis rates at 1 month, 0.5 and 0.2%, respectively. None of the other variables showed an advantage of thrombus aspiration.

At variance with results of prior smaller studies and meta-analyses, this large study shows no evidence of short-term mortality benefit for systematic thrombus aspiration prior to PCI for STEMI. Until longer

Specific lesion subsets

A major challenge in interventional cardiology is the percutaneous treatment of chronic total occlusions (CTO). Further to advanced techniques and novel equipment, improved results were shown in a meta-analysis of 18,061 patients from 65 studies demonstrating an overall angiographic success rate of 77% with low complication rates (MI 2.5%, coronary perforation 2.9%, cardiac tamponade 0.3%). Contrast-induced nephropathy occurred in 3.8%. Unsuccessful PCI in CTO had a higher mortality rate (1.5 vs. 0.4%, P < 0.0001).21

Percutaneous coronary intervention for acute coronary syndrome and STEMI

While PCI for high-risk non-ST segment acute coronary syndrome (NSTE-ACS) and STEMI is recommended as a life-saving procedure, several recently reported trials are challenging current recommendations regarding important procedural strategies: the use of mechanical thrombus aspiration, deferred PCI of non-culprit stenosis in patients with multivessel disease, and the use of intra-aortic balloon pump (IABP) for haemodynamic support in patients with cardiogenic shock.
follow-ups become available, TASTE challenges the level of the current recommendation to routinely perform mechanical thrombus aspiration prior to primary PCI. Pathophysiological studies have provided a better understanding of microvascular obstruction by embolization of debris and how it affects TIMI frame count and myocardial blush. Intramyocardial areas of microvascular obstruction, oedema, and haemorrhage can be identified using magnetic resonance imaging (Figure 2) by late gadolinium enhancement imaging (3) shows microvascular obstruction (arrow), consistent with the hypo-intense area of haemorrhage on T2w-image (4). Intramyocardial haemorrhage and microvascular obstruction are very comparable in size and location and show a close relationship. (Reprinted with kind permission from Reference 28, Eur Heart J 2013).

**Figure 2** Late gadolinium enhancement images (top row) compared with T2-weighed turbo-spinecho (T2w) images (bottom row) in one animal (1 and 2) and one PCI-treated STEMI patient (54-year-old male with anterior wall infarction). Cardiac magnetic resonance was performed 5 days after PCI. Late gadolinium enhancement imaging (3) shows microvascular obstruction (arrow), consistent with the hypo-intense area of haemorrhage on T2w-image (4). Intramyocardial haemorrhage and microvascular obstruction are very comparable in size and location and show a close relationship. (Reprinted with kind permission from Reference 28, Eur Heart J 2013).

Primary percutaneous coronary intervention and multivessel disease

The recently presented PRAMI trial (Preventive Angioplasty in MI trial) involved 465 patients with multivessel disease who were randomized 1:1 to PCI of the culprit stenosis only or to immediate PCI of all stenosis following successful primary PCI of the culprit occlusion. Primary endpoint of cardiac death, MI, or refractory angina with proven ischaemia was in favour of preventive angioplasty of non-culprit stenosis: 21 vs. 53% event rates, HR 0.35 (CI 0.21–0.58; P < 0.001). There was no increased safety hazard, and increase in procedure duration and radiation exposure seems to be acceptable. Superiority of the more invasive approach remained highly significant with secondary combined endpoint of death and MI at 11 vs. 27%, respectively (HR 0.36, CI 0.18–0.73; P = 0.004). Criteria that were used to identify suitable patients for inclusion in the trial as well as to identify which non-culprit lesions were suitable for immediate PCI need to be better understood before this approach can be generalized. These impressive results are calling for confirmation in a larger trial powered to confirm superiority of the ‘preventive’ angioplasty approach using a dual mortality and MI primary endpoint.
Balloon pump in cardiogenic shock

The negative results of the trials testing the usefulness of intra-aortic balloon counterpulsation (IABP) for haemodynamic support in cardiogenic shock patients have surprised many physicians. Primary endpoint, mortality at 30 days, in the SHOCK-IABP trial was entirely neutral between patients presenting with STEMI and cardiogenic shock randomized 1:1 to best of care, with ($n = 301$) or without ($n = 299$) IABP. No evidence of benefit accrued up to 1 year. Mortality in cardiogenic shock patients remained very high at 52 and 51%, with and without IABP (relative risk 1.01). Quality of life metrics in survivors were good, yet superimposable between randomization groups. Outcomes following cardiogenic shock are dismal and IABP does not appear to sufficiently support the failing circulation. The unmet need remains and urges the evaluation of more powerful assist devices.32

Prevention of ischaemic and reperfusion injury: role of pre- and post-conditioning

Pre- and post-conditioning as well as remote ischaemic pre-conditioning strategies have suggested positive effects on endpoints based on biomarker release or magnetic resonance imaging. At variance, pharmacological approaches using adenosine, cariporide, nicorandil, PKC-delta inhibitors, erythropoietin, and cyclosporine A have showed mixed result.33 From a pooled analysis of 10 randomized trials, ischaemic post-conditioning reduced myocardial enzyme leaks and preserved left ventricular ejection fraction.34 Remote ischaemic conditioning was tested in 333 STEMI patients during transportation to the primary PCI centre.35 Conditioning entails intermittent arm ischaemia through four cycles of 5-min blood-pressure cuff inflation followed by 5-min deflation. At 3.8 years follow-up, the primary composite endpoint—all-cause mortality, MI, readmission for heart failure, and ischaemic stroke were 13.5% in patients with remote ischaemic conditioning and 25.6% in the control group (HR 0.49, CI 0.27–0.89, $P = 0.018$). Obviously, these results need to be confirmed in larger populations. When proven useful, such simple measures could be implemented during pre-hospitalcare through the emergence of increasingly efficacious and well-organized STEMI networks.

New-generation drug-eluting stents, stent thrombosis, and coronary scaffolds

Drug-eluting stents

Meanwhile coronary stent implantation using DES has become a default therapy during PCI, with an increasing number of approved DES becoming available, and few undergoing extensive trial-based evaluation in large study populations. Given the good results obtained with second-generation DES, recent trials are designed to test non-inferiority, rather than superiority of the newer drug-polymer-device iteration.

The TWENTE trial randomized patients 1:1 between zotarolimus-eluting (ZES, Resolute) and everolimus-eluting stent (EES, Xience V). The primary endpoint was target vessel failure (TVF). At 1 year, the composite of cardiac death, TV-related MI, and clinically driven TV revascularization (TVR) reached 8.2% in the ZES and 8.1% in the EES arm, demonstrating non-inferiority.36 Meanwhile the 2-year results showed equal rates of TVF at 10.9 vs. 11.6% ($P = 0.65$) and similar MACE rates.37 The Dutch PEERS study (TWENTE II) compared 1:1 the ZES (Resolute) with the EES (Promus Element platinum chromium DES) in 1811 all-comer patients (2371 lesions). The primary endpoint of TVF was a composite of safety (cardiac death or TV-related MI) and efficacy (TVR) at 12 months (with a non-inferiority margin of 36%). The primary endpoint was met by 55 (6%) of 905 patients in the ZES and 47 (5%) of 905 in the EES stent group (absolute risk difference 0.88%, CI –1.24–3.01%; upper limit of one-sided 95% CI 2.69%; non-inferiority $P = 0.006$).38 An additional multicentre study reported the 2-year results of a pooled analysis looking at ZES (Resolute) for in-stent restenosis. The restenosis rate was 12.7% compared with 4.3% ($P = 0.003$) in patients with de novo stenosis. Cardiac death and TV-related MI did not differ significantly (6.9 vs. 6.1%).39 The final 5-year report for the LEADERS (Limus Eluted from A Durable vs. ERodable Stent coating) trial became available as well.40 Either a biodegradable polymer biolimus-eluting stent (BES) or a durable polymer sirolimus-eluting stent (SES, first generation Cypher, no longer available) was implanted in 2707 patients. Biolimus-eluting stent had a significant reduction of (very) late definite stent thrombosis from 1 to 5 years (0.6 vs. 2.2%, $P = 0.003$). The risk reduction was 0.26 (CI 0.10–0.69, $P = 0.0034$). Post-hoc comparison of cases with low and high SYNTAX scores showed similar reduction in definite stent thrombosis with BES. Biolimus-eluting stent (Nobori) and EES (Xience or Promus) were recently compared 2:1 in 2707 patients (4025 lesions). Cardiac death, non-fatal MI, and clinically indicated TVR at 12 months occurred in 93 (5.2%) patients in the BES group and 44 (4.8%) patients in the EES group (relative risk 1.07, CI 0.75–1.52, $P < 0.0001$, non-inferiority).41 Similar findings were reported by the NEXT investigators, who randomized 3235 patients 1:1 to receive BES or EES.42

Given the limited availability of large direct comparative studies between each new DES, network meta-analysis has been proposed as an alternative evaluation method. A recent network analysis evaluating the relative merits of paclitaxel-eluting stent (PES), SES, EES, ZES, and BES identified EES and ZES as the devices with highest safety profile.43 Whether newer generation DES, especially when the drug is released from bioerodable polymers show clinical advantages over EES or ZES that use more biocompatible durable polymers than first-generation DES, especially in the long term, remains undecided.

Stent thrombosis

A meta-analysis of four trials studied the clinical impact of extending dual antiplatelet therapy (DAPT) in 8231 randomized patients. The median DAPT time was 16.8 vs. 6.2 months for the control group. All-cause death, MI, stent thrombosis, or cardiovascular event rates were not reduced in the extended DAPT group.
However, extended DAPT increased the risk of major bleedings (HR 2.64, CI 1.1–5.3, P = 0.006).44

The PRODIGY (PROlonging Dual antplatelet treatment after Grading stent-induced Intimal hyperplasia study) trial studied the duration of DAPT (6–24 months) depending on type and potency of the implanted stent. In a randomized study, 2013 patients were treated with BMS, ZES, PES, or EES implantation. Patients receiving ZES showed a significantly higher rate of definite, probable, and possible stent thrombosis in the shorter DAPT group. No association was seen between stent potency for inhibition of intimal hyperplasia and greater vulnerability to shorter DAPT. The rate of death, MI, and cerebrovascular event were higher in the ZES group with longer DAPT therapy (HR 2.85, P = 0.0018).45 In 3119 patients with stable coronary artery disease or low-risk ACS treated with ZES, 3 months of DAPT (clopidogrel plus aspirin) was non-inferior to 12 months for the composite of all-cause death, MI, stroke, or major bleeding, without significantly increasing the risk of stent thrombosis [6.0 vs. 5.8%, respectively; risk difference, 0.17 (95% CI, −1.52–1.86); P = 0.002].46 A nation-wide retrospective cohort study of 29 268 patients was performed in Denmark in order to estimate the risk of stent thrombosis, when clopidogrel was discontinued after MI. All patients receiving clopidogrel after discharge from a first MI were included from 2004 to 2009.47 At 18 months follow-up, death and recurrent MI were observed in 3214 cases (11%). For those treated by PCI, the estimated incidence rate ratio of death or MI within the first 90 days following discontinuation was 1.59 (CI 1.11–2.30, P = 0.013). There was no such risk in patients treated medically only. Thus, discontinuation of clopidogrel therapy 1 year after PCI for MI was associated with an increased risk of death of a recurrent MI during the first 90 days following clopidogrel interruption.

The incidence and impact of DAPT cessation on adverse events following PCI was evaluated in the PARIS 5031-patients large real-world registry.48 The importance of the mode of cessation was evaluated, i.e. discontinuation (as recommended by the physician), interruption (a conscious decision guided by a physician), or disruption (patient stops because of bleeding or non-compliance). Rate of cessation of DAPT therapy was 2.9, 23.3, and 57.3% within 30 days, 1 year, and 2 years, respectively. Cardiac death, stent thrombosis, or MI were strongly associated with the mode of cessation with no increase risk in the case of discontinuation or interruption. Disruption, however, was associated with high risk of adverse events with significant HRs of 9.82 with DAPT cessation within 1 week, 2.98 with cessation within 30 days, and 1.71 beyond 30 days following PCI.

**Drug-eluting coronary scaffolds**

The year 2013 has seen the emergence of clinical application of bioerodable coronary scaffolds, in particular with the use of the everolimus-eluting Absorb device (BVS).49 While results of randomized evaluations of this technology are pending, numerous case reports and small series reporting on the feasibility of BVS use in various lesions and patient subsets have been released, including PCI for (N)STEMI.50–52 Confidence in the clinical performance of BVS has grown following extensive analysis of limited observational series but involving sequential multimodality evaluations using angiography, intravascular ultrasound, optical coherence tomography imaging, coronary vasomotor testing, and multislice coronary computed tomography.53 In addition to this specific brand, other bioerodable scaffolds may be entering the clinical scene.54,55 Because many announced that bioerodable scaffolds represent the future of coronary stenting, adoption of BVS by physicians and patients seems to have anticipated the available evidence, at least in areas with favourable regulatory environment. If the incremental value of bioerodable scaffolds over durable metallic stents stems primarily from their disappearance, clinically relevant benefit will only become apparent after long-term follow-up of large patient groups.

**Conclusion**

This overview is necessarily subjective but demonstrates the vitality of the clinical research in the field of PCI, and stresses areas where further investigation remains very active. Significant advances in the synergy between novel antithrombotic drugs and coronary devices, especially in patients with ACS, were reported in 2013, but not discussed here. Disruptive innovative technologies continue to be developed, with potential changes in clinical treatment strategies ahead. It is expected that even stronger emphasis will be placed on life-saving indications of PCI in patients with NSTE-ACS or STEMI, optimization of adjunctive medical therapy as well on the cost-effectiveness of PCI procedures in general.

**Conflict of interest:** R.E.: Travel expenses from Biotronik paid directly to private account. W.W.: Institutional research grants from pharmaceutical (AstraZeneca, Therabel) and device (Abbott Vascular, Biosensors, Biotronik, Boston Scientific, Cordis, Medtronic, Orbus Neich, St Jude, Terumo, Tryton) companies; honoraria and fees on behalf of W.W. go to the Cardiovascular Research Center Aalst. Co-founder and stockholder of Argonauts, Genae Americas, and Cardio3BioSciences.

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