The Year in Cardiology

The Year in Cardiology 2012: coronary intervention

Simon R Redwood*

BHF Centre of Excellence, King’s College London, St Thomas’ Campus, Westminster Bridge Road, London SE1 7EH, UK

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I am delighted to provide readers of the European Heart Journal with an overview of scientific data relating to Coronary Intervention in 2012. This article aims to summarize the important publications and presentations; it includes a summary of the main interventional meetings (ACC, EuroPCR, ESC, TCT, and AHA) together with a selection of important publications from the major general and specialist journals.

PCI in general

Throughout Europe there has been a move towards percutaneous coronary intervention (PCI) being performed in units without on-site cardiac surgery. In the UK, over 60% of units do not have on-site surgery and these units generally perform a lower volume of PCI than those with on-site surgery (median of 435 compared with 1454 procedures, respectively). The need for emergency surgery is now a very uncommon complication. The Atlantic CPORT Investigators randomized, in a non-inferiority design, nearly 19 000 patients undergoing PCI to a hospital with or without on-site surgery in a ratio of 1:3. Six-week mortality was virtually identical (1.0 vs. 0.9%) and 9-month major adverse cardiac events (MACE) were also similar (11.2 vs. 12.1%); however, target vessel revascularization (TVR) was higher without on-site surgery (6.5 vs. 5.4%, \( P = 0.01 \)). This difference was seen regardless of the definition of TVR and regardless of stent type and may reflect a more conservative approach or a lower initial success rate without on-site surgery. In the USA, a very small proportion of total PCI was performed without on-site surgery and it remains to be seen whether this study will alter that proportion.1

Public reporting of patient outcomes following PCI is an important tool to monitor the quality of care; however, it may lead some operators to become ‘risk-averse’. Joynt et al. reported a retrospective observational study of patients admitted with an acute coronary syndrome to US hospitals in states that do and in states that do not report outcomes publicly between 2002 and 2010. In 2010, ACS patients were less likely to receive PCI in public reporting states than in non-reporting states, and this difference was more marked for STEMI and cardiogenic shock (CS); however, there were no significant differences in mortality. Interestingly, in Massachusetts the odds of undergoing PCI for acute myocardial infarction (MI) fell after the introduction of public reporting. There are, of course, at least two explanations for why public reporting was associated with reduced PCI rates—either operators were more risk-averse or some procedures in non-reporting states are unnecessary and reporting of outcomes improves the appropriateness of PCI.2

The SYNTAX study suggested that patients randomized to coronary artery bypass surgery (CABG) had a higher risk of stroke, although the majority of that risk was in fact pre-surgery, implying that it was either a chance finding or related to stopping of anti-platelets pre-op. A meta-analysis of 19 randomized trials of over 10 000 patients found a 30-day rate of stroke of 1.2% after CABG and 0.34% after PCI (\( P < 0.0001 \)) This equates to an excess of seven strokes for every 1000 patients treated with CABG rather than PCI. Similar results were observed after a median follow-up of 1 year and in an analysis of nearly 34 000 patients from 27 observational studies.3

The FREEDOM trial results should be of great importance. This trial randomized 1900 diabetic patients with multi-vessel disease to PCI using drug-eluting stents (DESs) vs. CABG. At 5 years, the primary outcome of death, MI, or cerebrovascular accident (CVA) occurred more commonly in the PCI group (26.6 vs. 18.7%, \( P = 0.005 \)), driven by excess rates of both MI and death in the PCI arm; however, stroke was higher with CABG (Figure 1). These results serve as a wake-up call to Interventional Cardiologists considering revascularization options for any diabetic with more than single-vessel disease.4

The management of elective major non-cardiac surgery after coronary stent implantation remains an important issue in peri-operative care. Current guidelines generally recommend delaying surgery for

* Corresponding author. Tel: +44 207 188 1083, Fax: +44 207 401 3527, Email: simon.redwood@gstt.nhs.uk

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1 month following bare-metal stents (BMSs) and 1 year following DESs. Registry data were analysed in a cohort study of >8000 patients undergoing non-cardiac surgery and had received stents in the preceding 10 years, with a comparison of patients who had not undergone previous stenting. Although 1-month MACE was 2.1% in patients with coronary stents, if the interval was <45 days, event rates were 6.7% for BMSs and 20% for DESs. Between 45 and 180 days, the event rates were 2.6% for BMSs and nearly 4% for DESs. After 180 days, the rate for DESs was 1.2%. Thus, this analysis supports waiting for at least 45 days for elective non-cardiac surgery following BMSs but at least 180 days following DESs.5

**Appropriateness of PCI**

Recently, the ACC and AHA, in conjunction with five other societies, published appropriate use criteria for revascularization. Data from >8000 patients undergoing elective CABG and nearly 34 000 undergoing PCI were analysed to assess appropriateness. Only 1% of those undergoing CABG were deemed inappropriate, but 14% of PCI patients were inappropriate; furthermore 28% lacked enough non-invasive data to determine appropriateness. 6 Hannan et al.7 also compared outcomes of patients who did and those who did not undergo elective PCI from the New York database. Using propensity matching and a cohort of 933 matched pairs, outcome was determined; 89% of all patients underwent PCI. Compared with medically treated patients, PCI was associated with lower adverse outcomes at 4 years (for mortality, 10.2% vs. 14.5%; for subsequent revascularization, 24.1% vs. 29.1%).

There are also direct data supporting the use of ischaemia guidance (IG): in a 5000-patient registry, perfusion imaging (MPI) was performed in 42.3% and IG revascularization in 17.3% (12.4% in PCI and 21.8% in CABG). Major adverse cardiac and cerebral events was lower in the IG than in the non-IG group (16.2 vs. 20.7%), driven by lower repeat revascularization.8

The ASCERT study analysed elective revascularization strategies in nearly 200 000 over 65-year-old patients with two or three vessel disease undergoing CABG or PCI. One-year mortality was similar but at 4 years, mortality with CABG was lower than PCI (16.5 vs. 20.5%).9

The issue of completeness of revascularization following PCI was assessed by several studies. SYNTAX scoring was determined pre- and post-PCI in patients enrolled in the ACUITY study. A residual SYNTAX score of >0 was considered incomplete revascularization (IR). Thirty-day and 1-year ischaemic events were higher in the IR group. Residual SYNTAX score was an independent predictor of ischaemic events at 1 year, including mortality.10 In a separate analysis of these data, this association was also seen if IR was assessed by quantitative coronary angiography and variably defined according to different diameter stenosis cut-offs.11

**Physiological lesion assessment guidance**

The use of fractional flow reserve (FFR) to guide PCI is supported by robust clinical data and Pijls et al.12 published an excellent review. The FAME 2 trial assessed FFR in stable patients and those who had at least one significant lesion (FFR <0.8) were randomized to FFR-guided PCI or optimal medical therapy (OMT). The trial was halted after 880 patients were randomized. The primary endpoint of death, MI, or urgent revascularization was
4.3% in the PCI group and 12.7% in the OMT group (P < 0.001); this difference was due to higher urgent revascularization in the OMT group (Figure 2). There could, of course, have been some bias in recommending revascularization in patients in the OMT group with recurrent angina but these data do further support the routine use of FFR-guided procedures.13

At Transcatheter Cardiovascular Therapeutics (TCT), data were presented supporting the cost-effectiveness of this approach, although the trial randomized after the FFR measurements were made, so the cost of the wire was not taken into account. There are now some data emerging for a new method of determining functional significance using a pressure-sensor tipped wire without the need for vasodilatation. Using wave intensity analysis, a wave-free period in which intracoronary resistance at rest is similar in variability and magnitude to FFR was determined, known as the instantaneous wave-free ratio. Early studies suggest that it may be an alternative to FFR determined during vasodilatation,14 but this new index needs to be validated in larger cohorts of patients.

**Haemodynamic support**

The BCIS-1 trial previously reported no difference in early MACE for high-risk PCI patients randomized to intra-aortic balloon pump placement pre-PCI. However, the long-term mortality data were reported recently. At up to 5-year follow-up, there was a significant mortality advantage favouring upfront IABP insertion [hazard ratio (HR) 0.66, 95% CI: 0.44–0.98, P = 0.039], although the potential mechanisms of this remain unclear.15

The outcomes of CS over the time period 1995–2005 were compared in French registries. Over that time period, there was a small reduction in the incidence of CS (6.9–5.7%), and there was a substantial reduction in mortality in these patients, from 70 to 51%; this was associated with an increase in use of PCI from 20 to 50%, which was an independent predictor of survival.16

The role of haemodynamic support for CS was determined in the IABP-SHOCK II trial. Patients undergoing revascularization were randomized to IABP support (n = 300) or conventional treatment (n = 300). Thirty-day mortality was very similar in the two groups (39.7 vs. 41.3%, respectively). However, in the IABP group, only 13% were inserted pre-PCI. Thus, although this trial does not support IABP placement after revascularization, this was not a trial of IABP-supported PCI in CS.17

**Stents**

A meta-analysis of 72 randomized trials (>117 000 patients) looked at comparative outcomes of different DESs compared with BMSs. Everolimus DESs seemed to have the lowest TVR. Reassuringly,
there was no increased risk of any long-term safety outcomes with DESs compared with BMSs; in fact, DESs were associated with reduced MI and sub-acute thrombosis (SAT) rates. At TCT, the XIMA trial was presented. This trial randomized 800 patients over the age of 80 to either BMSs or DESs (Xience). The primary outcome of death, MI, TVR, CVA, or bleeding was non-significantly higher in the BMS group (18.7 vs. 14.5%, \( P = 0.092 \)), driven by an excess of TVR in that group. Importantly, bleeding was not increased with prolonged dual anti-platelet therapy (DAPT), suggesting that DESs are safe and effective in the elderly.

A report of the SCARR registry of over 94,000 patients found that newer generation DESs are associated with a 38% lower risk of clinical restenosis and a 43% lower risk of SAT compared with first-generation DESs.

The RESET trial compared everolimus with sirolimus DESs in a randomized non-inferiority trial of over 3000 patients. At 1 year, the primary endpoint of TLR occurred in 4.3 vs. 5.0% demonstrating non-inferiority. SORT OUT IV also compared these two stents in a non-inferiority design but with a composite primary endpoint of safety and efficacy. Just over 2700 patients were randomized. The composite endpoint was similar in the two groups at 9 and 18 months, but definite stent thrombosis was higher at 18 months with the sirolimus stent (0.9 vs. 0.2%).

The TWENTE trial randomized 1391 patients to zotarolimus (Resolute) vs. everolimus (Xience) stents in a non-inferiority design. The primary endpoint of target vessel failure (TVF) was similar in the two groups (8.2 vs. 8.1%), and stent thrombosis rates were low and similar.

A further comparison of everolimus and paclitaxel DESs was reported for left main interventions and again showed reduced 1-year MACE, TVF, and restenosis with everolimus DESs. In add-
tion, at TCT the ISAR-LEFT MAIN-2 trial was presented, and showed similar outcomes with everolimus compared with zotaro-
limus stents; however, TLR was disappointing at \( \sim 10\% \) —I wonder whether that would have been lower if they investigators had man-
dated the use of intravascular ultrasound (IVUS). An excellent review article on left main interventions was published by Teirstein et al. and is well worth looking at.

In a small mechanistic study, patients with in-stent restenosis (ISR) after DESs were randomized according to lesion length. In those with focal ISR, late lumen loss was higher following cutting balloon that sirolimus DES implantation. In those with diffuse ISR, sirolimus and everolimus stents were comparable.

Late (>10 year) outcomes of the first in man (FIM) non-drug-eluting biodegradable (Igaki-Tamai) stents were reported in 50 patients. All-cause survival was 87% and TLR was 16% and at 1 year and 28% at 10 years. Late thrombosis occurred in two patients. IVUS analysis showed that stent struts had largely disappeared by 3 years. External elastic lamina area did not change suggesting no significant late elastic recoil.

Complications of PCI

Stent thrombosis

In the largest head-to-head DESs trial to date, the PROTECT trial compared zotarolimus with sirolimus (Cypher) stents in nearly 9000 patients with duration of DAPT left to the discretion of the operator and showed no difference between the two stents in the primary endpoint of stent thrombosis at 3 years. However, in a prospective cohort study, of over 12,000 patients, the risk of last SAT was assessed and everolimus DESs were asso-
ciated with a lower very late thrombosis risk than either sirolimus or paclitaxel DESs (hazard ratio: 0.65). In a pooled analysis of ISAR-TEST 3 and 4 and LEADERS trials, the risk of SAT at 4 years with biodegradable polymer DESs was compared with that with a Cypher stent (a durable polymer); biodegradable polymer was associated with lower TLR and SAT (hazard ratio: 0.56), driven mainly by a reduction in very late SAT. In a meta-analysis of 50,000 patients, 1-year SAT was lowest with ever-
olimus DESs compared with BMSs, zotarolimus, paclitaxel, or sirol-
limus DESs.

Duration of DAPT was investigated in several studies. In the 1443 patient EXCELLENT non-inferiority randomized study of 6 months vs. 12-month DAPT after DESs, 1-year TVF occurred in 4.8 vs. 4.3%, respectively. However, this study was not powered to look at death or MI and in the diabetic subset, TVF occurred more frequently in the 6-month group (HR: 3.16; CI: 1.42–7.03, \( P = 0.005 \)). A further study of 2000 patients com-
pared 3–12-month DAPT following zotarolimus DESs and found no difference in SAT (0.2 vs. 0.3%) at 1 year. The PRODIGY trial randomized 2000 patients to either 6- or 24-month DAPT following a variety of BMSs or DESs. Interestingly, using a composite endpoint of death, MI or stroke, there was no difference between short or prolonged duration DAPT in any group.

Reassuringly, in a study of over 1600 patients, investigators assessed the risks of temporary discontinuation of DAPT within the first year following DESs. Overall, 10.6% interrupted DAPT beyond the first month for a median of 7 days and this was not associated with an increase in MACE.

Thus, second-generation DESs seem to have lower SAT rates and there are now data supporting safety of shorter duration DAPT, at least in non-diabetics.

Acute kidney injury

Contrast-induced nephropathy (CIN or AKI) is associated with a significant increase in short- and long-term morbidity and mortality. Various measures have been used to limit its occur-
rence, including sodium bicarbonate infusion. This was tested in a randomized trial of 258 patients against a similar volume of sodium chloride infusion. Change in glomerular filtration rate was more in the bicarbonate group. Previous studies have failed to conclusively support N-acetyl cysteine. In a separate study, the risk of AKI after cardiac surgery was not found to be influenced by timing between coronary angiography and surgery. At TCT, the POSEIDON trial was presented and showed that LVEDP-guided hydration was superior to standard hydration in preventing AKI in patients with stable renal impair-
ment. Thus, it seems that limitation of contrast volume and ade-
quate hydration, perhaps with the rate guided by weight and LVEDP measurement, are the most-effective strategies for pre-
venting AKI.
Bleeding post-PCI

Using the CathPCI Registry, post-PCI bleeding was found to reduce by 20% over the years 2005–09, and this seemed largely due to changes in anti-thrombotic strategies with a reduction in GPIb/IIa use and an increase in bivalirudin use. Radial access accounted for 1–2%; in contrast to some previous studies, vascular closure devices seemed to be associated with a small reduction in bleeding.36

Varying bleeding definitions make comparisons of different studies troublesome; the Bleeding Academic Research Consortium proposed standardized definitions in order to address this. These were validated in a pooled analysis of over 12,000 patients from six randomized trials. Bleeding Academic Research Consortium Class >2 was associated with an increase in 1-year mortality, supporting the use of these definitions in outcome trials.37

Acute myocardial infarction

Intracoronary abcximab but not thrombectomy was found to reduce infarct size in the 450-patient INFUSE-AMI trial.38 In contrast to this, a retrospective analysis of over 2500 patients found higher TIMI 3 flow rates and better survival in those who had thrombectomy.39 In a 2000-patient randomized trial, intracoronary, and i.v. abcximab were compared. The primary endpoint of death, recurrent MI, or CCF was similar in the two groups, although there was a small reduction in CCF associated with the intracoronary route and there was no difference in safely. A meta-analysis also supported these results.40 Thus, abcximab seems to reduce infarct size and the route of administration does not seem to be important. The role of routine thrombectomy remains uncertain.

The use of DESs in acute MI remains controversial, and this year several comparisons were reported. Bare-metal stents were compared with biolimus biodegradable polymer stents in a 1100-patient randomised trial. One-year MACE was lower with the biolimus stent, a difference driven mainly by a reduction in re-infarction and TLR.41 In a 1500-patient trial, everolimus DESs were compared with BMSs; the primary endpoint of death, recurrent MI, or revascularisation was similar in the two groups. However, TLR rates were lower with the everolimus stent (3.7 vs. 6.8%), as was SAT (0.9 vs. 2.5%).42 In a meta-analysis of 15 trials with nearly 8000 patients, early-generation DESs reduced TLR compared with BMSs, but this benefit was offset by an increased risk of very late SAT.43 Finally, a comparison of first-generation (sirolimus) and second-generation (everolimus) stents was reported. In a 625-patient non-inferiority trial, MACE at 1 year was lower with the everolimus stent (4 vs. 7.7%).44 SAT was also lower with everolimus, although not significantly, and this would need to be confirmed in larger trials. Thus, DESs do reduce restenosis and the newer generation DESs may reduce the increased risk of late SAT.

The issue of access site for STEMI PCI was raised at TCT; the STEMI-RADIAL trial randomized 700 patients to either a radial or femoral approach. Interestingly, the radial approach was associated with less contrast use and shorter ICU stays. The primary endpoint of bleeding or access-site complications was dramatically lower with the radial approach and MACE was equivalent. Although 2b3a use was relatively high, this does support the radial approach in experienced hands (excuse the pun!) (Figures 1 and 2).

Conclusions

2012 has been a busy and productive year in coronary intervention! It is hoped that this brief summary will help inform the reader and stimulate them to delve more deeply into the publications and presentations highlighted.

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CARDIOVASCULAR FLASHLIGHT

Giant left ventricular aneurysm as a late complication of inferior myocardial infarction

Francis J. Alenghat1, Gregory S. Couper2, and Michael M. Givertz1*

1Cardiovascular Division, Department of Medicine, Brigham and Women’s Hospital, and Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA; and
2Division of Cardiac Surgery, Department of Surgery, Brigham and Women’s Hospital, and Harvard Medical School, Boston, MA, USA

* Corresponding author. Tel: +1 617 732 7367, Fax: +1 617 264 5265, Email: mgivertz@partners.org

After 3 days of nausea and dyspnoea, a 62-year-old man was found to have a completed inferior myocardial infarction. Angiography demonstrated right coronary artery occlusion, and no intervention was performed. Several days later, he had worsened dyspnoea and syncope due to pericardial haematoma. This prompted emergent surgical evacuation and patch repair of a 2-cm inferior wall rupture.

Three months later, he presented with fatigue, a displaced point of maximal impulse, a holosystolic murmur, and a visually pulsatile abdomen above the umbilicus. An electrocardiogram showed inferolateral Q waves and persistent inferolateral ST-segment elevations. An echocardiogram demonstrated severe left ventricular dilation (Figure 1A), an ejection fraction of 25%, and severe mitral regurgitation (Figure 1B). Cardiac MRI demonstrated a giant inferior/inferolateral aneurysm extending from the mitral annulus to near the apex, as shown in long axis (Figure 1C, and see Supplementary material, Videos S1 and S2). The aneurysm dwarfed the ventricle’s non-aneurysmal portion, with LV end-diastolic and end-systolic volumes of 840 and 740 mL, respectively. The patient underwent ventricular reconstruction, mechanical mitral valve replacement, and left anterior descending coronary artery bypass (of a 70% stenosis). Intraoperatively, the 2-mm thick aneurysmal wall had well-defined borders and included part of the postero medial papillary muscle. The previously placed patch and surrounding aneurysmal wall were excised, and a triangular Dacron patch was placed to exclude the scar completely and substantially reduce the LV size, as seen by transoesophageal echocardiogram (Figure 1D, arrow marks patch and see Supplementary material, Videos S3 and S4). Confirming true aneurysm, histology demonstrated transmural infarction. The patient also received an implantable cardioverter-defibrillator for primary prevention.

Although indications for ventricular reconstruction are debatable, this extremely large aneurysm caused severe mitral regurgitation and heart failure symptoms. Six months later, the patient’s ejection fraction improved to 43% and he was feeling well and enjoying exercise without residual symptoms.

Supplementary material is available at European Heart Journal online.