The year in cardiology 2014: coronary intervention

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Preamble

Interventional cardiology is a dynamic specialty with ongoing innovations to improve the devices and active research to enable practicing evidence-based medicine. This article summarises the main highlights of interventional cardiology research in the year 2014, particularly focusing on myocardial revascularisation for stable angina and acute coronary syndromes, adjunctive pharmacotherapy for patients undergoing percutaneous coronary intervention, and clinical trials of coronary stents and bioresorbable scaffolds.

Introduction

The year 2014 has brought several innovations and new data from trials on myocardial revascularisation, coronary stents and scaffolds, adjunctive pharmacological therapy, and treatment of coronary atherosclerosis and acute coronary syndromes. This article summarises the most pertinent studies of the year of 2014.

Myocardial revascularization

An important progress this year was the development of new joint ESC-EACTS Guidelines on Myocardial Revascularization taking into account the novel data published in the recent years.1

Percutaneous coronary intervention vs. coronary artery bypass grafting

The final 5-year results of the SYNTAX trial were published in January 2014. This year has seen a number of post-hoc studies from this trial. For the unprotected left main stem (LMS) cohort (n = 705), no difference in overall major adverse cardiac and cerebrovascular events was found between the groups treated with coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI) using the first-generation paclitaxel-eluting stent.2 Percutaneous coronary intervention-treated patients had a lower risk of stroke but a higher revascularization rate vs. CABG. It is recommended that LMS patients with low and intermediate (0–32) SYNTAX score may be considered for PCI, whereas for patients with high (>32) SYNTAX score CABG is recommended.3 For patients with three-vessel disease, CABG should remain the standard therapy for intermediate and high (>22) SYNTAX score patients, whereas PCI is an acceptable revascularization strategy for patients with low (0–22) SYNTAX scores.4 Figure 1 shows the comparison of PCI vs. CABG for patients with three-vessel disease in the SYNTAX trial. It appears that SYNTAX score 2 incorporating anatomical and clinical variables is more helpful than the anatomical SYNTAX score for decision-making for revascularization strategy.4 A network meta-analysis of 100 trials in 93 553 patients with 262 090 patient-years of follow-up showed that CABG reduces the risk of death, myocardial infarction (MI), and subsequent revascularization compared with medical treatment. Percutaneous coronary intervention, compared with medical treatment, reduces the need for revascularization; however, only newer generation drug-eluting stents (DES) but not bare-metal stents or the first-generation DES improved survival.5 Therefore, unless concerns about dual-antiplatelet therapy (DAPT), newer-generation DES should be the default device for PCI.

Fractional flow reserve-guided percutaneous coronary intervention

The FAME-2 trial has demonstrated that fractional flow reserve (FFR)-guided PCI, when compared with medical therapy alone, improved the primary outcome of all-cause death, myocardial infarction (MI), or urgent revascularization by 61% (P < 0.001) in patients with stable coronary artery disease.6 Landmark analysis from 8 days till 2 years shows a significant reduction in death and MI (HR 0.56, 95% CI 0.32–0.97, P = 0.002).6 Patients without ischaemia had a favourable outcome with medical therapy alone.6

Revascularization for acute myocardial infarction

Percutaneous coronary intervention remains the treatment of choice for patients with ST-elevation myocardial infarction (STEMI) and appropriately risk stratified non-ST-elevation MI (NSTEMI) patients. Radial access should be the preferred approach as it reduces major...
bleeding and access site complications; this message is further consolidated in STEMI-RADIAL trial. Stenting should be preferred over balloon angioplasty in the setting of primary PCI. The newer generation DES are safe and effective in STEMI patients; a recent report from SCAAR registry has also shown that patients treated with newer-generation DES have a lower risk of early/late stent thrombosis than patients treated with bare metal stents. Unlike the case with early devices, the risk of very late ST was low and comparable between the two groups at 3-year follow-up.

**Thrombus aspiration**

The role of manual thrombus aspiration has remained controversial; however, TASTE (Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia) trial has shown no benefit or harm of routine manual thrombus aspiration compared with PCI alone in patients with STEMI at 1-year follow-up. The TATORT-NSTEMI (Thrombus Aspiration in Thrombus Containing Culprit Lesions in Non–ST-Elevation Myocardial Infarction) trial also showed that aspiration thrombectomy in conjunction with PCI in NSTEMI with a thrombus-containing lesion does not lead to a reduction in microvascular obstruction. Therefore, routine use of thrombus aspiration does not appear to be necessary but selected use may be useful to improve flow or prevent stent thrombosis.

**Fractional flow reserve guidance in acute myocardial infarction**

Whilst the role of FFR in guiding PCI is well established in patients with stable coronary disease, the value of FFR has not been specifically evaluated in patients with acute coronary syndrome (ACS).
The FAMOUS-NSTEMI trial randomized 350 patients referred for invasive management to FFR-guided PCI (n = 176) or standard angiography-guided management (n = 174). Fractional flow reserve was measured in both groups in all coronary arteries with stenosis ≥30% and normal blood flow. An FFR-guided strategy changed the initial treatment plan in approximately one-fifth of cases and resulted in a larger proportion (P = 0.02) of patients treated medically (23%) compared with an angiography-guided strategy (13%). Further larger trials powered to address clinical outcomes will determine whether FFR-guided strategy can be routinely recommended in ACS patients.

Culprit lesion vs. multivessel percutaneous coronary intervention

In the acute setting of STEMI, current guidelines favour the treatment of culprit lesions only in patients undergoing primary PCI and future revascularization of non-culprit lesions for symptomatic or prognostic indications. In January 2014, PRAMI (Randomized Preventive Angioplasty in Acute Myocardial Infarction) trial (n = 465) suggested that preventive PCI in non-infarct-related arteries with ≥50% stenosis in the acute setting may be associated with a reduced risk of the composite of death, MI, or refractory angina (HR 0.35, 95% CI 0.21–0.58, P < 0.001). CvLPRIT (Complete vs. Lesion-only Primary PCI Trial), presented at ESC this year, randomized 296 STEMI patients to culprit-only (n = 146) vs. complete revascularization during the index procedure or same admission (n = 150). At 12-month follow-up, patients in the complete revascularization group had significantly better outcomes than those who had culprit-lesion revascularization (MACE: 10.0% vs. 21.2%, P = 0.009). At present, multivessel PCI during primary PCI should be considered in patients with cardiogenic shock in the presence of multiple, critical stenoses, or highly unstable lesions (angiographic signs of possible thrombus or lesion disruption), and if there is persistent ischaemia after PCI on the supposed culprit lesion. The ideal timing of non-culprit lesion revascularization in patients with STEMI, i.e. during primary PCI vs. staged procedure, needs to be explored further. On-going COMPLETE (Complete vs. Culprit-only Revascularization to Treat Multi-vessel Disease After Primary PCI for STEMI) trial with larger sample size may provide data to settle this important issue.

Percutaneous coronary intervention adjunctive therapy

Antiplatelet therapy

Clopidogrel remains the preferred P2Y12 inhibitor for patients undergoing PCI for stable angina. For non-ST-elevation ACS patients, prasugrel can be used for clopidogrel naïve patients scheduled for PCI, whereas ticagrelor can be used for all patients regardless of the treatment strategy. For STEMI patients undergoing PCI, either prasugrel or ticagrelor can be used. The ATLANTIC trial has shown that pre-hospital compared with in-hospital (a median time of only 31 min later then pre-hospital) administration of ticagrelor in patients with STEMI does not improve pre-PCI coronary reperfusion, but it does appear safe and may reduce post-procedural definite acute stent thrombosis. Further data from real-world registries (with potentially longer time difference between pre-hospital and in-hospital administration) are needed to evaluate the merit of pre-hospital treatment strategy.

The duration of DAPT has also been further explored in randomized trials in 2014. The ARCTIC-Interruption study evaluated DAPT beyond 1 year after DES implantation and found no significant benefit in low-risk patients and increased risk of bleeding events. Unfortunately, no conclusions can be drawn about high-risk patients. SECURITY and ISAR-SAFE trials have shown that 6-month DAPT is non-inferior to 12-month DAPT for patients undergoing PCI with the newer-generation DES. The recently published DAPT (Dual Antiplatelet Therapy Beyond One Year After Drug-eluting Coronary Stent Procedures) trial randomized 9961 patients to receive thienopyridine or placebo along with aspirin for an additional 18 months after completing 1 year of dual-antiplatelet therapy for DES implantation. Patients assigned to continued thienopyridine had a significantly lower incidence of stent thrombosis (0.4 vs. 1.4%, P < 0.001) and MI (2.1 vs. 4.1%, P < 0.001), but higher rates of moderate/severe bleeding (2.5 vs. 1.6%, P = 0.001). There was no difference in cardiovascular mortality; however, all-cause mortality (2.0 vs. 1.5%, P = 0.05) was higher with continued DAPT. A potential concern about oncolgical deaths needs further exploration.

From these trials, it appears that patients with high risk of bleeding may safely stop DAPT at 6 months, whereas patients with higher ischaemic/thrombotic and lower bleeding risk should continue DAPT beyond 12 months; an individualized risk–benefit assessment is vital.

Anticoagulant therapy

Adjunctive anticoagulation therapy for patients undergoing PCI has remained a hot topic in 2014. Earlier trials in STEMI patients have shown that bivalirudin may be preferred over combination of unfractionated heparin and glycoprotein inhibitors (GPIs). The recent EUROMAX study comparing bivalirudin (n = 1089) with heparin plus routine upstream GPI (n = 649) or heparin plus bailout GPI (n = 460) also suggested superiority of bivalirudin. The primary outcome of death and major bleeding occurred in 5.1% with bivalirudin, 7.6% with heparin plus routine GPI (HR 0.67, 95% CI 0.46–0.97, P = 0.034), and 9.8% with heparin plus bailout GPI (HR 0.52, 95% CI 0.35–0.75, P = 0.006). However, there was no mortality benefit and stent thrombosis rates were higher with bivalirudin. Further trials have even questioned the efficacy of bivalirudin.

BRAVE-4 (Bavarian Reperfusion Alternatives Evaluation) trial aimed to compare prasugrel plus bivalirudin (n = 271) against clopidogrel plus unfractionated heparin (n = 277) in STEMI patients undergoing primary PCI. The primary endpoint of death, MI, unplanned revascularization of the infarct-related artery, stent thrombosis, stroke, or major bleeding at 30 days was similar between the two groups (Figure 2); however, it is important to highlight that this trial was terminated early and was underpowered. HEAT-PPCI (How Effective Are Antithrombotic Therapies in Primary PCI), a single-centre, randomized, controlled trial compared with bivalirudin and bailout GPI with unfractionated heparin and bailout GPI among STEMI patients undergoing primary PCI. The primary efficacy outcome of all-cause mortality, stroke, reinfarction, or unplanned
revascularization occurred in 8.7% of the bivalirudin group vs. 5.7% of the heparin group ($P = 0.01$). Stent thrombosis was also more common in the bivalirudin group (3.4 vs. 0.9%, $P = 0.001$). The primary safety outcome of major bleeding occurred in 3.5% of the bivalirudin group vs. 3.1% of the heparin group ($P = 0.59$). It is recommended that all patients undergoing primary PCI should receive anticoagulation along with antiplatelet therapy; however, the choice of anticoagulant can be tailored according to the ischaemic and bleeding risk of an individual patient.$^1$

**Stents and scaffolds**

**Newer-generation drug-eluting stents**

The newer-generation DES have consistently shown superiority over the first-generation DES. The PROTECT trial compared ENDEAVOR zotarolimus-eluting stent with CYPHER sirolimus-eluting stent. There was no difference in the primary outcome of definite or probable stent thrombosis at 3 years. However, at 4-year follow-up published this year, the primary outcome occurred in 1.6% of ENDEAVOR vs. 2.6% of CYPHER patients (HR 0.63, 95% CI 0.46–0.85, $P = 0.003$). The composite of all-cause death or MI occurred in 6.7% of ENDEAVOR vs. 8.0% of CYPHER treated patients (HR 0.84, 95% CI 0.71–0.98, $P = 0.024$). Similarly, SORT-OUT III had shown superiority of CYPHER compared with ENDEAVOR at 1-year follow-up (MACE: HR 2.13, 95% CI 1.48–3.07, $P < 0.0001$) but no difference at 5 years (MACE: HR 1.10, 95% CI 0.88–1.37, $P = 0.40$). At 1 year, definite stent thrombosis was more frequent in the ENDEAVOR group (HR 3.34, 95% CI 1.08–10.3, $P = 0.036$), whereas opposite finding was recorded between 1- and 5-year follow-up (HR 0.05, 95% CI 0.01–0.36, $P = 0.003$). In the SORT-OUT IV trial, XIENCE everolimus-eluting stent was non-inferior to CYPHER sirolimus-eluting stent at 9 months. At 3-year follow-up, the MACE rate did not differ significantly between the two groups; however, a significant reduction of overall and very late definite stent thrombosis was found in the XIENCE group.$^2$ In the RACES-MI trial, no significant difference was observed between XIENCE and CYPHER stents in major adverse cardiac events (MACE, 16 vs. 20.8%, HR 0.75, 95% CI 0.5–1.13, $P = 0.17$), cardiac death (4.4 vs. 5.6%, HR 0.77, 95% CI 0.35–1.71, $P = 0.53$) and target vessel revascularization (4.8 vs. 4.8%, HR 1.00, 95% CI 0.45–2.32, $P = 0.99$). However, XIENCE stents were associated with a significant reduction in stent thrombosis (1.6 vs. 5.2%, HR 0.3, 95% CI 0.1–0.92, $P = 0.035$).$^{22}$

HOST-ASSURE (harmonizing optimal strategy for treatment of coronary artery stenosis-safety and effectiveness of drug-eluting stents and anti-platelet regimen) trial randomized 3755 all-comers receiving PCI to platinum chromium-based everolimus-eluting (PROMUS ELEMENT) stent or cobalt chromium-based zotarolimus-eluting (RESOLUTE) stent. At 1 year, there was no difference in target lesion failure (TLF: 2.9 vs. 2.9%, superiority $P = 0.98$, non-inferiority $P = 0.025$) or its components between the two groups.$^{23}$ Of 5010 stents analysed, longitudinal stent deformation occurred in 0.2% and 0% in the PROMUS ELEMENT and RESOLUTE groups, respectively ($P = 0.104$). In the DUTCH-PEERS trial, 1811 patients were randomized to receive either RESOLUTE or PROMUS ELEMENT.$^{24}$ There were no significant differences in the composite endpoint of target vessel failure, its individual components, and definite stent thrombosis. Longitudinal stent deformation was seen only in the PROMUS ELEMENT group (1.0 vs. 0%, $P = 0.002$), but was not associated with any adverse events.$^{24}$ The trials comparing the newer-generation DES among themselves have not shown a definite superiority of one stent over the others.

**Biodegradable vs. durable polymer**

A number of trials have compared the DES that release the drug from either biodegradable or durable polymer. The CENTURY II (Clinical Evaluation of New Terumo Drug-Eluting Coronary Stent System in the Treatment of Patients with Coronary Artery Disease) trial compared safety and efficacy of a new sirolimus-eluting stent with biodegradable polymer (ULTIMATSER) against everolimus-eluting stent with durable polymer (XIENCE).$^{25}$ At 9-month follow-up, there was...
no difference in TLF (Figure 3). The stent thrombosis rate was 0.9% in both groups.25 The NEXT trial comparing biolimus-eluting stent with biodegradable polymer (NOBORI) against everolimus-eluting stent with durable polymer (XIENCE or PROMUS) has shown non-inferiority of NOBORI stent at 2-year follow-up.26 The BIOSCIENCE trial comparing an ultra-thin strut biodegradable polymer sirolimus-eluting stent (ORSIRO) vs. durable polymer everolimus-eluting stent (XIENCE) has also shown no difference in TLF (6.5 vs. 6.6%, non-inferiority P = 0.0004) or stent thrombosis at 12 months.27 However, in STEMI sub-group, ORSIRO stents were associated with improved outcome.27 The I-LOVE-IT 2 trial comparing sirolimus-eluting biodegradable (TIVOLI) vs. durable polymer (FIREBIRD) stents also showed no difference in the primary endpoint of TLF (6.3 vs. 6.1%, non-inferiority P = 0.0002) at 12 months.28 Whether biodegradable polymer improves safety with respect to lowering late stent failure and thrombosis compared with durable polymer remains to be shown at longer-term follow-up.

Bioresorbable scaffolds

There have been a number of small-scale clinical studies and registries suggesting efficacy and safety of bioresorbable scaffolds. ABSORB-II is the first randomized trial comparing an everolimus-eluting biodegradable scaffold (335 patients, 364 lesions) against an everolimus-eluting metallic stent (166 patients, 182 lesions).29 The acute recoil post-implantation was similar (0.19 mm for both, P = 0.85); however, acute lumen gain was lower for the bioresorbable scaffold by quantitative coronary angiography (1.15 mm vs. 1.46 mm, P < 0.0001) and quantitative intravascular ultrasound (2.85 vs. 3.60 mm², P < 0.0001), resulting in a smaller lumen diameter or area post procedure. At 1-year, however, cumulative rates of first new or worsening angina from adverse event reporting were lower (22 vs. 30%, P = 0.04), whereas performance during maximum exercise and angina status by Seattle Angina Questionnaire were similar. The 1-year composite device oriented endpoint was similar between the bioresorbable scaffold and metallic stent groups (5 vs. 3%, P = 0.35). Three patients in the bioresorbable scaffold group had definite or probable scaffold thrombosis, compared with no patients in the metallic stent group.29 Longer follow-up is needed to show the potential advantages of the bioresorbable scaffolds in preventing very late stent thrombosis.30

Bioresorbable scaffolds have also been tested in patients with STEMI. BVS STEMI first, POLAR ACS, and PRAGUE-19 studies have shown the feasibility and safety of these devices in patients with STEMI.31,32 Further data with larger sample size and longer follow-up are needed. It remains to be investigated which patient and/or lesion subsets will benefit more from treatment with bioresorbable scaffolds, instead of metallic stents.

Atherosclerosis

A few studies have investigated various pharmacological interventions for plaque regression and primary or secondary prevention of coronary events.

Statins

The IBIS-4 study evaluated the effect of long-term high-intensity statins on plaque burden, composition, and phenotype in non-infarct-related arteries of STEMI patients undergoing primary PCI.33 Patients were treated with rosuvastatin (40 mg/day) throughout 13 months and serial intracoronary imaging with the analysis of matched segments was available for 82 patients with 146 non-infarct-related arteries (Figure 4). After 13 months, the atheroma volume decreased by −0.9% (95% CI 1.56 to −0.25, P = 0.007). Majority (74%) of the patients had regression in at least one artery. Necrotic core remained unchanged (−0.05%, 95% CI −1.05 to 0.96%, P = 0.93) as did the number of thin cap fibroatheromas (124 vs. 116, P = 0.15).33

High-density lipoprotein raising agents

Other studies investigating novel therapeutic agents have generally yielded negative results. CHI-SQUARE (Can Hdl Infusions Significantly QUicken Atherosclerosis REgression) study investigated the effects of an high-density lipoprotein (HDL)-mimetic agent CER-001 on atherosclerosis but failed to show any effect by intravascular ultrasonography and quantitative coronary angiography.34 The HPS2-THRIVE study randomly assigned 25 673 adults with vascular disease to receive extended-release niacin and laropiprant or a matching placebo daily.35 During a median follow-up period of 3.9 years, niacin–laropiprant therapy had no significant effect on the incidence of major vascular events (13.2 vs. 13.7%, P = 0.29) and was associated with serious adverse events.35

Darapladib

Studies with darapladib, an inhibitor lipoprotein-associated phospholipase A2 (Lp-PLA2), added to statin therapy, have shown no benefit in large randomized clinical trials. The STABILITY (Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) trial randomly assigned 15 828 patients with stable coronary disease to receive extended-release niacin and laropiprant or a matching placebo daily.36,37 During a median follow-up period of 3.9 years, niacin–laropiprant therapy had no significant effect on the incidence of major vascular events (13.2 vs. 13.7%, P = 0.29) and was associated with serious adverse effects.35

Figure 3 Comparison of biodegradable and durable polymer stents in the CENTURY-II trial. Kaplan–Meier curves of the cumulative event rates for target lesion failure for biodegradable polymer sirolimus eluting stent (BP-SES) vs. permanent polymer everolimus eluting stent (PP-EES). Reproduced from Saito et al.25
Darapladib added to optimal medical therapy and initiated within 30 days of hospitalization, however, did not reduce the risk of major coronary events during 2.5-year follow-up.37

Proprotein convertase subtilisin/kexin type 9 inhibitors

Inhibition of proprotein convertase subtilisin/kexin type-9 (PCSK-9) by monoclonal antibodies represents a novel therapeutic approach to treat hyperlipidaemia. In the LAPLACE-2 trial, evolocumab added to moderate- or high-intensity statin therapy over a 12-week period resulted in additional lowering of low-density-lipoprotein cholesterol (LDL-C) in patients with primary hypercholesterolaemia and mixed dyslipidaemia.38 The DESCARTES trial has also shown that evolocumab added to diet alone, to low-dose atorvastatin, or to high-dose atorvastatin with or without ezetimibe significantly reduced LDL-C levels in patients with a range of cardiovascular risks at 52-week follow-up.39 Similar results have been shown in the GAUSS-2, MENDEL-2, OSLER, and ODYSSEY trials. At ESC 2014, preliminary findings from a post-hoc analysis of ODYSSEY LONG TERM trial in 2341 patients with hypercholesterolaemia and very high cardiovascular risk has shown a 61% reduction in LDL-C with alirocumab compared with placebo. Furthermore, there was a 54% reduction in MACE (defined as cardiac death, non-fatal MI, ischaemic stroke, and unstable angina requiring hospitalization) over the 65 weeks (HR 0.46, 95% CI 0.26–0.82, P < 0.01).

These promising results merit further studies to evaluate longer-term clinical safety and efficacy of PCSK-9 inhibitors in reducing cardiovascular outcomes.

Conclusion

This overview is not comprehensive for all interventional cardiology research in 2014 but highlights the major advancements. Percutaneous coronary intervention continues to challenge the superiority of CABG in treating patients with complex coronary artery disease. Newer drug-eluting stents have generally shown an improvement in long-term outcomes. This year has also seen significant advancement in adjunctive pharmacotherapy, enabling physicians to adopt an evidence-based therapy tailored to individual patients’ thrombotic and bleeding risk. Biodegradable polymers and biodegradable scaffolds have shown promising results. However, long-term data in large study groups are now needed to demonstrate incremental benefit of novel device-based therapies on currently achievable outcomes.

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