Special Article

Almanac 2012: Interventional Cardiology. The National Society Journals Present Selected Research That has Driven Recent Advances in Clinical Cardiology

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The field of interventional cardiology continues to progress quickly. The efficacy of percutaneous interventions with newer generation drug-eluting stents has advanced a lot over the last decade. This improvement in stent performance has broadened the level of indication towards more complex interventions such as left main and multi-vessel PCI. Major improvements continue in the field of medical co-therapy such as antiplatelet therapies (bivalirudin, prasugrel, ticagrelor) and this will further improve outcomes of PCI. The same is true for intravascular imaging such as ultrasound (IVUS) and optical coherence tomography (OCT). However, interventional cardiology has become a rather broad field, also including alcohol septal ablation for hypertrophic obstructive cardiomyopathy, etc. At the moment, the fastest growing area is the structural interventions, especially for aortic valve stenosis (transcatheter aortic valve implantation, TAVI) and for mitral regurgitation (mitral clipping). This review covers recent advances in all these different fields of interventional cardiology.

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This review covers recent advances in different fields of interventional cardiology, including percutaneous interventions with newer generation drug-eluting stents, medical co-therapy, intravascular imaging, and other, broader applications.

Percutaneous coronary intervention versus medical treatment

Percutaneous coronary intervention (PCI) has guideline recommendations for treatment of ST elevation and non-ST elevation myocardial infarction (MI).[1] However, its role in stable coronary disease has been the subject of reappraisal following publication of the COURAGE trial, which showed that, in patients receiving optimal medical therapy, PCI does not improve cardiovascular outcomes, while incremental benefits for quality of life disappear by 36 months.[2,3] A more recent meta-analysis of eight trials of optimal medical therapy versus PCI involving 7229 patients bears out the COURAGE conclusions by showing no significant differences between the groups with regard to death (9.1% vs. 8.9%), non-fatal MI (8.1% vs. 8.9%), unplanned revascularisation (30.7% vs. 21.4%) and persistent angina (33% vs. 29%).[4] Drug-eluting stents (DESs) were used in only a minority of these patients and may have reduced the need for further revascularisation while improving symptomatic responses. Nev-

ertheless, the meta-analysis reinforces contemporary guideline advice for optimal medical treatment as the initial treatment for stable angina.[5] Whether this will change current practice remains to be seen, but early signs are not encouraging. Thus a US registry analysis of patients undergoing PCI before (n=173,416) and after (n=293,795) the COURAGE report showed no change in the proportions receiving optimal medical treatment (43.5% vs. 44.7%).[6]

PCI versus coronary bypass surgery

The safety of PCI at hospitals without on-site cardiac surgery has been confirmed in two recent reports.[7,8] Add to this the feasibility of PCI in increasingly complex disease and we need look no further to explain the substantial reductions in rates of coronary bypass surgery (CABG) in recent years. A recent US study of revascularisation procedures during 2001-2008 showed a 38% decline in rates of CABG, while PCI decreased by only 4%.[9] Some have questioned whether patients are being appropriately advised according to contemporary guidelines,[10] a US analysis of 500,154 PCIs reporting that, among the 28.9% of cases performed for non-acute indications, only 50.4% were appropriate and that angina was not present in many of the inappropriate cases.[11] In the absence of any evidence of prognostic benefit, there can be no indication for PCI in stable patients without angina. In patients with angina, on the other hand, PCI is as effective as CABG in providing symptom relief at 12 months, judging by a recent report from the SYNTAX investigators.[12] However, CABG may have the advantage of providing prognostic benefit, recent US registry data showing a lower 4-year mortality compared with PCI (16.4% vs. 20.8%) in an analysis that adjusted for selection bias.[13] Of course, being a registry study, treatment allocation was not random and any conclusions about relative prognostic benefits require caution. Nevertheless, guideline recommendations are for surgery in complex three-vessel and left main stem disease, although many patients continue to express a preference for PCI, particularly now we have reports of the feasibility and safety of same-day discharge. This is particularly applicable with radial access (or post-procedural deployment of a femoral closure device), and, in a US registry study, 1339 patients discharged on the same day as their procedure had similar 30-day readmission rates to 105,679 patients who stayed overnight.[14] This is important because it is now recognised that readmission within 30 days after PCI is associated with a significant increase in 1-year mortality.[15]

Left main stem disease

The trespass of PCI on to territory that was formerly surgical is best illustrated by its increasing application in unprotected left main stem disease. Registry data from the USA for 131,004 patients with unprotected left main stem disease show the proportion treated with PCI increasing from 3.8% to 4.9% between 2004 and 2008. PCI recipients were older with more comorbidities, probably accounting for their higher hospital mortality compared with the overall cohort (13% vs. 5%).[16] Technical improvements since 2008 have seen further increases in rates of PCI in unprotected left main stem disease, and we now have randomised trial data confirming its safety and efficacy in selected patients. Thus in the Korean PRECOMBAT trial of drug-eluting stenting versus CABG in 600 patients, 8.7% of patients in the stent group and 6.7% in the CABG group met the primary end point (a composite of death, MI, stroke and ischaemia-driven revascularisation at 12 months), a difference significant for the non-inferiority of stenting.[17] As in previous randomised comparisons, the difference was driven largely by a higher rate of repeat revascularisation in stent recipients (9.0% vs. 4.2% after 2 years, p=0.02). Selection for revascularisation in left main stem disease has traditionally been based on angiographic assessment, but a recent study suggests that measurement of minimum lumen area by intravascular ultrasound (IVUS) might be a better means of selection in patients with 'intermediate' angiographic stenoses in the range 25-60%.[18] Correlation between minimum lumen area and angiographic stenosis was poor, but a 6 mm^2 area measurement provided a safe threshold for determining revascularisation, the event-free survival being no worse in the patients with an area measurement >6 mm^2 who did not undergo revascularisation compared with the patients with an area measurement <6 mm who did. These were non-randomised data, but point to a useful role for IVUS in the management of left main coronary artery disease.

DESs and stent thrombosis

The introduction of bare metal stents (BMSs) towards the end of the last decade dramatically improved the performance and safety of PCI, but it required drug-eluting technology to make a significant

impact on restenosis rates. Concerns about an increased risk of stent thrombosis with DESs[19] appear to have been exaggerated, particularly with the current generation of DESs, but the beneficial effects on restenosis have been borne out. Thus a recent meta-analysis comparing sirolimus-eluting and bare metal stents in patients with diabetes reported dramatic reductions in the need for repeat revascularisation with the DES (HR 0.27, 95% CI 0.18 to 0.41) without any increase in the risk of stent thrombosis.[20] However, it has been the everolimus-eluting stent that has emerged as the interventionists' favourite, a meta-analysis of 13 randomised trials including 17,101 patients reporting thrombosis rates of only 0.7% during 21.7 months' follow-up, compared with 1.5% in patients treated with any other type of DES.[21] A further meta-analysis pooled data from 49 randomised trials including 50,844 patients and came to similar conclusions by showing that everolimus-eluting stents had the lowest risk of stent thrombosis at 30 days and 1 year compared with other stents approved for use in the USA, including BMSs.[22] The difference in favour of everolimus-eluting stents remained significant at 2 years when the odds of stent thrombosis was 0.34 (95% CI 0.19 to 0.62) compared with paclitaxel-eluting stents and 0.35 (95% CI 0.17 to 0.69) compared with BMSs.

Data on DESs in saphenous vein grafts are somewhat less clear, but the limited available randomised trials do suggest superiority compared with BMSs.[23] For primary PCI, concerns that the thrombotic environment might predispose to DES thrombosis have not been fully realised, a pooled analysis of 15 STEMI trials comparing first-generation DESs with BMSs reporting a lower requirement for target vessel revascularisation with DESs (RR 0.51, 95% CI 0.43 to 0.61), with no difference in the rate of stent thrombosis compared with BMSs.[24] Indeed, the risk of stent thrombosis during the first year was reduced for DESs (RR 0.80, 95% CI 0.58 to 1.12) but increased thereafter (RR 2.10, 95% CI 1.20 to 3.69), suggesting that the early benefit of first-generation DESs in primary PCI is offset by a later increase in the risk of stent thrombosis. Newer-generation DESs may overcome this drawback, but, until we have sufficient data, operators should carefully weigh the differential risk of restenosis and stent thrombosis between the two stent types.

Interest in bioresorbable stents has been enhanced by reports from a phase II evaluation of imaging data 12 months after implantation in 56 patients.[25] The restenosis rate was only 3.5%, and >95% of the stent struts were endothelialised. Moreover, variable coronary dilatation in response to acetylcholine was observed, indicating some return of normal vasomotor responses. The results of randomised trials now in the planning stage are eagerly awaited.

Optimal arterial access

Radial access for coronary angiography has now achieved widespread application.[26,27] One reason is the accumulating evidence that it reduces bleeding risk and, perhaps because of this, may reduce mortality in primary PCI.[28] Thus a comprehensive meta-analysis pooling all the data from randomised primary PCI trials comparing femoral with radial access showed a nearly 50% mortality reduction in the radial group.[29] Whether this beneficial effect is generalisable to everyday clinical practice is unclear, but observational data support the trial results and indicate benefit of radial access for primary PCI.[30,31] Another potentially important advantage of radial access is its association with a reduced risk of kidney injury, as reported in a large Canadian study of 69,214 patients undergoing cardiac catheterisation.[32] The mechanism is unclear and the largest trial comparing radial and femoral access, the RIVAL trial, did not show a clear advantage for either access route, although radial access appeared preferable in the subgroup undergoing primary PCI.[33] On the basis of current evidence, the choice between radial and femoral access should be individualised taking into account operator experience, bleeding risk and patient preference.

Antiplatelet therapies–what's new?

In patients undergoing PCI, dual antiplatelet therapy with aspirin and clopidogrel remains central to guideline recommendations. For clopidogrel, a pooled analysis of available data favoured a loading dose of 600 mg, which was associated with a 34% reduction in the rate of major adverse cardiac events (MACE) without any increase in the risk of major bleeding compared with a 300 mg loading dose.[34] Now we have randomised trial evidence confirming that, compared with the 300 mg loading dose, the 600 mg dose in primary PCI is associated with significant reductions in infarct size, measured by median CKMB mass over 72 h (2070 vs. 3029 ng/mL).[35] Continuing therapy with aspirin and clopidogrel is usually recommended after PCI in both stable and pa-

tients with acute coronary syndromes (ACS), but the antiplatelet effect of clopidogrel is variable, and high on-treatment platelet reactivity can be demonstrated in 14.7-26.9% of patients, depending on the test used.[36] Part of this variability in antiplatelet responsiveness is explained by the fact that clopidogrel is a prodrug, and the enzymes that form its active metabolites exhibit functionally distinct polymorphisms. However, a study from the Netherlands of 1069 clopidogrel-pretreated patients undergoing elective PCI found that loss-of-function CYP2C19 carrier status explained only part of the variability in platelet reactivity (13.0-20.6%), depending on the test used.[37] One approach to modifying high on-treatment platelet reactivity in carriers of loss-of-function CYP2C19 variants is to use antiplatelet drugs metabolised by different pathways, and this was confirmed by investigators from Korea in a substudy of the CILON-T randomised trial.[38] In patients with loss-of-function CYP2C19 variants who were randomised to dual antiplatelet therapy plus cilostazol, a selective phosphodiesterase-3 inhibitor, on-treatment platelet reactivity was significantly reduced compared with patients who received only aspirin and clopidogrel. This effect of cilostazol was not seen in non-carriers of the loss-of-function polymorphism. An alternative approach for modifying high on-treatment platelet reactivity after PCI is to increase the dose of clopidogrel. However, this was found ineffective in the GRAVITAS trial, the 6-month rate of the composite of cardiovascular death, MI and stent thrombosis being identical for groups randomised to high-dose (150 mg daily) or standard-dose (75 mg daily) clopidogrel.[39]

Current guideline recommendations are for clopidogrel to be stopped 12 months after DES deployment when endothelialisation is complete, reducing the risk of thrombosis. Worryingly, a clustering of late clinical events has been associated with this policy, perhaps because of an increase in arachidonic acid-induced platelet activation as reported in a recent UK study,[40] lending support to the accumulating evidence that clopidogrel exerts some of its antiplatelet effects via this pathway, independently of aspirin. Indeed, it has been suggested that discontinuation of aspirin instead of clopidogrel might be more rational 1 year after stenting.[41] This question will soon be tested in the large GLOBAL-LEADERS randomised trial. The limitations of dual antiplatelet therapy with aspirin and clopidogrel have been further illustrated by the on-TIME-2 trial, in which patients undergoing primary PCI were randomised to additional prehospital tirofiban or placebo.[42] The addition of tirofiban produced more effective platelet inhibition than aspirin and clopidogrel alone, and this was associated with a reduction in MACE and early stent thrombosis. On-TIME-2 lends further support to guideline recommendations for early glycoprotein IIb/IIIa inhibition together with dual antiplatelet therapy in patients undergoing primary PCI.

Newer P2Y12 receptor inhibitors

These include prasugrel and ticagrelor, which now have guideline indications in ACS[43] based on the TRITON and PLATO randomised trials, which were the subject of recent review.[44] TRITON randomised patients undergoing PCI for ACS to either clopidogrel or prasugrel therapy for 12 months after the procedure.[45] Prasugrel showed superiority over clopidogrel for the composite primary end point, driven mainly by periprocedural MI. It also showed significant risk reduction for stent thrombosis. However, these benefits came with an increased risk of major and minor bleeding. In the PLATO trial of ticagrelor versus clopidogrel in patients with ACS managed medically or with PCI,[46] ticagrelor was superior with regard to the primary composite end point of MACE, but, while minor bleeding was more common with ticagrelor, the major bleeding risk was comparable to that with clopidogrel. These randomised trials have confirmed that more intensive platelet inhibition with prasugrel or ticagrelor delivers better clinical outcomes in ACS, although there is a bleeding penalty, particularly it seems for prasugrel. The clinical outcome advantage for both drugs is small in absolute terms, raising important questions about cost-effectiveness. A US evaluation for prasugrel concluded it was 'an economically attractive treatment strategy',[47] but a more recent National Institute for Health and Clinical Excellence (NICE) technology assessment was more guarded, recommending prasugrel as an option in patients with STEMI if immediate primary PCI is necessary (based on its rapid onset of action compared with clopidogrel), or if diabetes is present or if stent thrombosis has occurred during clopidogrel treatment.[43] However, concern was expressed about its likely cost-effectiveness in other situations. A recent health-economic analysis based on the PLATO study concluded that treating patients with ACS with ticagrelor for 12 months is associated with a cost per QALY (quality-adjusted life year) below generally accepted thresholds for cost-effectiveness.[48]

Bivalirudin and heparin

Bivalirudin is now available for treatment of ACS and has rapidly gained a central role in primary PCI.[49] It is a direct thrombin inhibitor with additional activity against thrombin-mediated platelet activation that showed superiority over a combined regimen of heparin plus a glycoprotein IIb/IIIa inhibitor in HORIZONS-AMI, due largely to a lower rate of major bleeding (4.9% vs. 8.3%). All-cause mortality was lower at 30 days, and we now have 3-year follow-up data confirming persistent mortality benefit (5.9% vs. 7.7%), ensuring a guideline recommendation for bivalirudin in primary PCI.[50] The clinical benefits of bivalirudin have also been associated with cost-effectiveness, patient lifetime costs in the UK being £267 lower than for glycoprotein IIb/IIIa inhibitors.[51] A small increase in rates of stent thrombosis with bivalirudin was not seen in patients pretreated with heparin, and the mortality benefits of combining bivalirudin with heparin pretreatment have since been reported from the SCAAR registry,[52] leading the editorialist to recommend dual therapy in patients undergoing primary PCI.[53]

Unfractionated heparin retains a class 1 recommendation for use during PCI, but a recent meta-analysis of pooled data from 23 studies has shown that enoxaparin is associated with significant reductions in the composite of death and MI and in major bleeding rates compared with unfractionated heparin.[54] These benefits were greatest for primary PCI, but were also seen in PCI for non-ST elevation MI and stable angina. The time may be right for a change of policy in favour of low-molecular-weight heparin during PCI.

Intravascular imaging–clinical benefit?

The clinical benefit of using IVUS to guide PCI remains controversial, although a pooled analysis of seven randomised BMS trials has concluded that IVUS-guided PCI is associated with a reduced risk of in-stent restenosis.[55] IVUS is also finding a role in assessing left main stem lesions for revascularisation. As a research tool, however, and for validation of non-invasive imaging of coronary stenosis, IVUS has proved particularly valuable.[56] Thus, in a recent study comparing coronary CT angiography and IVUS for plaque volume measurements, there was only modest agreement between the two methods (Bland–Altman limits of agreement -67 to +65 mm^3), reflecting the limitations of coronary CT for assessing the extent of coronary disease.[57] While the ability to image across the coronary arterial wall is a particular strength of IVUS, the technology is limited by image resolution, which is considerably inferior to optical coherence tomography (OCT). In a substudy of ODESSA, for example, suboptimal stent deployment was identified by OCT at the level of individual stent struts, a detail that could never be reproduced by IVUS.[58] Increasingly, OCT is being used to assess stent strut endothelialisation, a recent Japanese study of everolimus-eluting stent implantation showing that, of 5931 struts assessed, 98.4% were endothelialised 8 months after implantation, an observation reflected in the low thrombotic risk for these second-generation DESs.[59]

Intravascular imaging has also been used to assess plaque stability, the PROSPECT trial confirming that IVUS can differentiate stable from unstable plaque and predict adverse events.[60] A key feature of unstable plaque is thin-cap atherosclerosis, and recent data remind us that the inflammatory environment is an important determinant of instability, an OCT study showing a clear association between the cap thickness of plaques and inflammatory plasma markers such as high-sensitivity C-reactive protein.[61]

Technical aspects of stenting–what have we learnt?

Overlapping stents

Re-endothelialisation of overlapping stent segments is slower, and most operators prefer single stent deployment for that reason.[58] However, in the real world, overlapping stent deployment is often unavoidable, and, for DESs, the conventional wisdom has been that homogeneous stents should be used to avoid elution of different pharmacological compounds within the overlapping segment. This has now been challenged by a Korean study of 1080 patients who received overlapping DESs.[62] The study showed that cardiac death, MI or target lesion revascularisation occurred with similar frequency regardless of whether the DESs were homogeneous or heterogeneous.

Bifurcation stenting

Several studies have shown that a single, main vessel stent deployment provides outcomes that are comparable – and often superior – to two-stent deployment. Thus a combined analysis of the NORDIC Bi-

furcation Study and the British Bifurcation Coronary Study showed that, in patients randomised to 'simple' main vessel stenting, the composite MACE end point at 9 months occurred in 10.1% of patients compared with 17.3% of patients who underwent complex two-vessel stenting (p=0.001).[63] However, questions remain, particularly concerning the value of final kissing balloon inflations across the bifurcation following main-vessel stenting. This was addressed in a large observational study of 1055 patients undergoing bifurcation stenting.[64] A comparative propensity analysis of patients who did and did not have final kissing balloon inflations showed a higher incidence of MACE and target lesion revascularisation, mostly in the main vessel, for patients who had final kissing balloon inflations. The pendulum therefore has now swung away from final kissing balloon inflation, which may cause more harm than good.

Myocardial infarction–high-sensitivity troponin assays

Central to the diagnosis of acute MI is the demonstration of a raised and changing troponin concentration in the first 24 h after symptom onset. The availability of high-sensitivity troponin (hsTn) assays is likely to see diagnostic thresholds fall, with important implications for clinical management and cardiac outcomes. Thus, in a recent study in which hsTn-I was measured in 1038 patients with suspected ACS, values below the previous limit of detection (0.20 ng/mL) showed graded association with death or non-fatal MI.[65] In a further 1054 patients, the diagnostic threshold was lowered to 0.05 ng/mL, and attending physicians were invited to modify their management accordingly. Rates of death and recurrent MI fell from 39% to 12% among patients with troponin concentrations 0.05-0.19 ng/mL, levels that would have been undetectable with conventional troponin assays. The investigators concluded that lowering the diagnostic threshold using hsTn assays has the potential to identify many high-risk individuals with suspected ACS and produce major improvements in their prognosis.

It has always been the recommendation that the diagnostic threshold level chosen for troponin should be based on a coefficient of variation of <10%, but new guidance is for the 99th centile value to be adopted regardless of assay imprecision.[66] The potential clinical impact of this change in guidance was evaluated in the same cohort as reported previously,[65] this time using a diagnostic threshold of 0.012 μg/L (coefficient of variation 20.8%).[67] At 1 year, patients with troponin concentrations of 0.012-0.049 μg/L, who previously would have escaped a diagnosis of MI, were more likely to be dead or readmitted with recurrent MI than those with troponin concentrations <0.012 μg/L (13% vs. 3%, p<0.001). The authors concluded that lowering the diagnostic threshold to the 99th centile and accepting greater assay imprecision would identify more patients at high risk of recurrent MI and death, but increase the diagnosis of MI by 46%. It remains to be established whether reclassification of these patients and treating them according to conventional MI guidelines will improve their outcomes.

hsTn assays will not only cause diagnostic thresholds for acute MI to fall, but may also allow identification of patients with apparently stable coronary disease who have vulnerable coronary lesions.[68] Thus a recent study has shown a strong correlation between hsTn-T and non-calcified plaque burden (r=0.79, p<0.001) in 124 patients with stable angina undergoing CT angiography, patients with remodelled non-calcified plaque having the highest hsTn-T values.[69] hsTn assays have already found clinical application for the early diagnosis of MI in patients with chest pain attending the emergency department. In the Randomised Assessment of Treatment using Panel Assay of Cardiac Markers (RATPAC) trial, the use of hsTn-I within a panel of biomarkers allowed successful discharge of 32% of patients compared with 13% of patients receiving standard diagnostic procedures.[70] Beyond their central role for diagnosis, troponins also provide a measure of the severity of MI, and, in a report from the GRACE registry,[71] incorporating 16,318 patients with non-ST elevation MI, each 10-fold increase in the troponin ratio was associated with stepwise increments in ventricular arrhythmias, heart failure, cardiogenic shock and death.[72]

Non-culprit lesions in ACS

The importance of myocardial salvage during the acute phase of infarction is emphasised by the fact that prognosis is driven largely by ultimate infarct size. We could therefore hypothesise that treating all significant lesions is beneficial. One of the first primary PCI randomised trials testing this hypothesis was reported last year. Among 214 patients with multivessel disease, adverse event rates during a mean follow-up of 2.5 years were higher with culprit-only PCI compared with multi-vessel PCI, whether performed

during the index procedure or as a staged procedure afterwards.[73] However, the trial was small and not definitive, a more recent meta-analysis finding in favour of culprit-only primary PCI with a staged strategy for non-culprit lesions.[74] This has become the guideline recommendation and was further supported by analysis of observational data from the HORIZONS-AMI trial in which outcomes for 275 patients treated with single-procedure stenting were compared with outcomes for 393 patients treated with staged procedures.[75] The single-procedure group received significantly more stents yet had a significantly higher 12 month mortality (9.2% vs. 2.3%) than the staged procedure group. The weight of evidence is now firmly in favour of culprit-only stenting during primary PCI.

Infarct size and myocardial salvage

Circadian rhythms in the onset of MI are well established, the morning hours being the period of greatest risk. Intriguingly, infarct size appears to show similar circadian variation, a retrospective analysis of 811 patients with STEMI showing that creatine kinase (CK) and troponin I curves peak between 06:00 h and noon.[76] Myocardial salvage in response to reperfusion therapy with PCI is the major strategy for limiting infarct size therapeutically and can now be quantified by cardiovascular magnetic resonance (CMR). A study of 208 patients presenting with STEMI confirmed that the extent of salvage measured by CMR is closely related to long-term prognosis, patients with a myocardial salvage index (MSI) above the median level having a lower number of adverse cardiovascular events (7 vs. 26) and deaths (2 vs. 12) after 18.5 months than patients with MSI below the median level.[77] Myocardial reperfusion, however, can itself exacerbate injury, by a variety of mechanisms which include interstitial haemorrhage. This can be detected by CMR and was reported in 25% of patients with STEMI treated successfully by primary PCI.[78] The presence of haemorrhage was an independent predictor of adverse remodelling, as reflected by increased left ventricular (LV) end-systolic volume at 3 months. The importance of interstitial haemorrhage as a predictor of LV remodelling was emphasised by the improvement in the area under the receiver operating characteristic curves from 0.699 to 0.826 when it was added to LV ejection fraction and infarct size in the predictive model. Microvascular obstruction after primary PCI is also predictive of remodelling, and in another CMR study was found to correlate significantly with reperfusion haemorrhage ($r^2=0.87$, $p<0.001$).[79]

Strategies to protect against reperfusion injury remain high on the research agenda and have been the subject of recent review.[80] In one study the effect of erythropoietin was tested based on beneficial experimental effects for reducing infarct size.[81] However, the study was negative, with patients randomised to erythropoietin (50,000 IU) before primary PCI showing an increased incidence of microvascular obstruction and LV dilatation without reduction in infarct size compared with patients randomised to placebo. Another study using forearm plethysmography tested a bradykinin B2 receptor antagonist, based on the hypothesis that endogenous bradykinin is a mediator of reperfusion injury.[82] The investigators found that remote ischaemic preconditioning abolished the impairment of endothelium-dependent vasomotor function induced by plethysmography, but bradykinin receptor blockade had no effect. Nevertheless, the finding that conditioning stimuli provide a clinically applicable means of protection against reperfusion injury was not new and has been replicated in other more recent clinical trials. A comparative primary PCI study of post-conditioning by staccato reversus abrupt reperfusion, for example, showed that the staccato protocol was associated with better preservation of microvascular function and LV dimensions 12 months later.[83] Staccato reperfusion was also partially effective in another primary PCI study in which patients were randomised to staccato reperfusion versus control. Infarct size was unaffected, except in patients with large areas at risk in whom it was significantly reduced by post-conditioning.[84]

The benefits of intra-aortic balloon counterpulsation (IABC) when cardiogenic shock complicates acute MI are generally accepted. Recently, the role of IABC for reducing infarct size in haemodynamically stable patients with anterior MI was tested in a randomised trial of 337 patients.[85] Infarct size at 3-5 days determined by MRI showed no significant difference between the groups, but those patients randomised to IABC showed a trend towards more vascular complications. The authors concluded that IABC produces no clinical benefit in this group of patients.

Contrast-induced acute kidney injury (CI-AKI)

Whether newer contrast agents, such as iso-osmolar contrast, have an impact on the CI-AKI risk is controversial.[86] Risk of CI-AKI is particularly high in pa-

tients presenting with an ACS, and recent data confirm it has a significant impact on clinical outcomes, including length of hospital stay and mortality.[87,88] The ACS setting offers little time to apply reno-protective measures, and strategies requiring up to 12 h of prehydration are clearly impractical. The need for a change in practice was emphasised by Wi et al,[87] who concluded that renal function should be measured at baseline and after primary PCI, to refine risk stratification. Meanwhile consideration should be given to reno-protection with bicarbonate, which has been reported to be more effective than normal saline using short-infusion or single-bolus protocols.[89] In certain subgroups, such as patients requiring urgent surgery for infective endocarditis, preoperative coronary angiography does not appear to increase the risk of acute kidney injury,[90] but, in general, contrast exposure should be kept at as low a level as possible during primary PCI. Meanwhile, randomised trials testing short-duration prehydration protocols or bolus applications of potentially reno-protective substances are needed.

Carotid artery stenosis–is stenting still an option?

Lifestyle adjustment and secondary prevention drugs may not always be effective in protecting against progression of carotid atherosclerosis. A recent trial of weight reduction with rimonabant, for example, reported that a 5% reduction in body weight over 30 months failed to influence the progression of carotid disease compared with patients who received placebo.[91] Many patients therefore require an interventional solution to their carotid disease, but whether this should be surgical or percutaneous remains contentious.[92] A large randomised trial of 2502 patients with symptomatic or asymptomatic carotid stenosis showed no significant difference in the estimated rates of the primary composite end point (periprocedural stroke, MI, or death or any ipsilateral stroke within 4 years) and no differential treatment effect by symptomatic status.[93] However, a recent meta-analysis pooling data from 11 randomised trials comparing carotid endarterectomy (CEA) with carotid artery stenting (CAS) showed that the periprocedural risk of mortality or stroke was lower for CEA (OR 0.67, 95% CI 0.47 to 0.95), mainly driven by a decreased risk of minor stroke, whereas the risk of death or disabling stroke was similar between the two groups. The odds of periprocedural MI or cranial nerve injury were significantly higher in the CEA group.[94] Current NICE guidelines recognise CAS as a treatment option for patients with symptomatic carotid artery stenosis, but emphasise that patients need to understand the risk of stroke and other complications associated with this procedure. Patient selection should be carried out by a multidisciplinary team.[95]

For asymptomatic carotid artery disease, the situation is even less clear. We know that patients with carotid stenosis undergoing cardiac surgery for their coronary artery disease have an increased periprocedural stroke risk and probably should be considered for treatment even if asymptomatic. The American guidelines recommend CEA if the stenosis is >80%, either before or combined with CABG. CAS before CABG is an alternative option with good results in patients who are considered 'high risk' for CEA.[96] Attempts to refine risk prediction in such patients have been the subject of considerable research, a recent carotid ultrasound study reporting that the total plaque area (HR 1.29, 95% CI 1.08 to 1.55), the number of plaques (HR 1.14, 95% CI 1.02 to 1.27) and the number of segments with plaque (HR 1.45, 95% CI 1.09 to 1.93) were all significantly associated with the 5-year risk of cerebrovascular events.[97]

Transcatheter aortic valve implantation

Transcatheter aortic valve implantation (TAVI) in older high-risk patients has yielded excellent results in most centres, the 2-year follow-up of patients in the PARTNER trial supporting the procedure as an alternative to surgery in high-risk patients.[98] Thus improvement in valve areas was similar for TAVI and for surgery, with comparable rates of death and stroke during follow-up. However, paravalvular regurgitation was more common after TAVI and has been associated with significantly worse outcomes, the German registry reporting higher in-hospital mortality, even after multivariate adjustments for potential confounders (OR 2.50, 95% CI 1.37 to 4.55).[99] Another cause for concern is the potential for myocardial injury during TAVI, as evidenced by elevations of CK-MB in 77% of 101 patients undergoing uncomplicated procedures.[100] Median maximal CK-MB levels were higher for transapical than trans-femoral access (22.6 μL vs. 9.9 μL), but were unaffected by the presence of coronary artery disease. Elevations of cardiac troponin T were also observed and were predictive of cardiac death at 9 months. Clearly, therefore, TAVI, like surgery, is commonly associated with some degree of myocardial injury that is not be-

nign. In most other respects, however, TAVI appears safe and has been associated with important symptomatic benefits, as reflected in the improvement in health-related quality of life reported by the PARTNER investigators.[101] Smaller studies have reinforced these findings by reporting improvement in the 6 min walk distance and quality of life scores, while brain natriuretic peptide (BNP) levels decline substantially.[102] Add to this the cost-effectiveness of TAVI in US and UK analyses, and it seems certain that indications will continue to expand.[103,104] Indeed, off-label TAVI is commonplace, with reported outcomes that are comparable to on-label procedures.[105] Paradoxically, increasing TAVI activity appears to have led to a significant increase in referrals for surgical aortic valve replacement,[106] with Manchester, for example, seeing a 37% increase in surgical AVR activity within the 2 years of starting a TAVI programme.[107]

Percutaneous mitral valve repair

The development of percutaneous systems for mitral valve repair in patients with severe mitral regurgitation has proved more challenging than TAVI. NICE gave a guarded verdict on the MitraClip device in 2010, recommending it only be used with 'special arrangements for clinical governance, consent and research for patients who are well enough for surgical mitral valve leaflet repair'.[108] This was based on the findings of the Endovascular Valve Edge-to-Edge REpair Study (EVEREST) investigators in an observational study of 107 patients with moderate or severe mitral regurgitation, which reported a successful MitraClip implant in 74% of patients, of whom 66% achieved freedom from death, mitral valve surgery and severe mitral regurgitation (≥3+).[109] Since then the EVEREST investigators have undertaken a further observational study in 78 older patients at high risk of conventional surgery, which showed that the MitraClip device reduced mitral regurgitation in the majority of patients, with improvement in symptoms associated with significant LV reverse remodelling over 12 months.[110] The benefits of the MitraClip appear closely related to its efficacy in reducing mitral regurgitation, the midterm outcomes showing significant association with the acute haemodynamic response.[111]

Alcohol septal ablation in hypertrophic cardiomyopathy

Three studies have recently reported longer-term outcomes after alcohol septal ablation in symptomatic patients with hypertrophic cardiomyopathy (HCM). The results have been encouraging. Among 874 patients with class III or IV symptoms in a US study, six (0.7%) died in relation to the procedure, and survival estimates at 1, 5 and 9 years were 97%, 86% and 74%, respectively.[112] Symptoms improved to class I or II in all but 5% of cases, although 13% required repeat ablation and 3% required surgical myomectomy. In a Canadian study of 649 patients with HCM, 38% were managed conservatively, and 62% underwent invasive therapy with alcohol septal ablation (21%), surgical myomectomy (71%) or dual chamber pacing (8%).[113] In multivariate analysis, invasive therapy was independently associated with better overall survival (HR 0.6; 95% CI 0.4 to 0.97, p=0.04), but not with HCM-related survival. Among the invasive group, the pacemaker-treated group fared less well than patients treated with septal ablation or myomectomy, questioning the call for a reappraisal of pacemaker therapy in a recent Spanish study that reported favourable long-term results in a group of 50 patients.[114] Finally, a Scandinavian study reported marked reductions in outflow tract gradients in response to 313 ablation procedures in 279 patients with HCM, of whom 94% had class III/IV symptoms.[115] Only 21% had class II/IV symptoms at 1 year, with little change thereafter. Estimated survival rates at 1, 5 and 10 years were 97%, 87% and 67%, respectively, and were comparable to survival rates in an age- and gender-matched population. Taken together, these studies testify to the long-term benefits of alcohol septal ablation in HCM, which appears to be a valid alternative to surgery in symptomatic HCM that does not respond to medical therapy.

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