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Stable coronary artery disease*

The National Society Journals present selected research that has driven recent advances in clinical cardiology

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Stable Angina Pectoris

Diagnostic strategies

The widespread application of specialist clinics for early evaluation of patients with chest pain has focused attention on the effectiveness of diagnostic testing. In a study of nearly 400,000 patients with suspected coronary artery disease, the diagnostic yield of cardiac catheterisation was only 37.6%, leading to calls for better strategies for risk stratification.[1] As pointed out in correspondence, the low yield was likely due to verification bias, itself a consequence of basing referral decisions in low risk populations on non-invasive tests such as the exercise ECG.[2] It was similar considerations that prompted recent guideline recommendations for a more selective approach to non-invasive testing based on a careful clinical assessment of disease probability in patients presenting with stable chest pain.[3] For those, with unequivocal histories at the extremes of diagnostic probability (<10% or >90%) no diagnostic tests were considered necessary, while for patients with a high probability of disease (60% to 90%) invasive angiography without prior ischaemia testing was the recommendation. The call for CT calcium scoring in patients with a low (10% to 30%) probability of disease generated particular concern after a recent study

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reported that up to 19% of patients without coronary calcification may have obstructive (>50% stenosis) disease.[4] However, the population referred for angiography in this study had a high pre-test probability of disease and in lower risk populations CT calcium scoring retains a high diagnostic sensitivity.[5] Whether it will improve the diagnostic yield of cardiac catheterisation remains to be seen.

Circulating biomarkers in stable angina

The clinical application of circulating biomarkers for diagnosis of obstructive coronary artery disease in patients with suspected angina has yet to be defined. In one study, blood samples for the N-terminal fragment of the prohormone brain natriuretic peptide (NT-proBNP) and various inflammatory markers were obtained in 243 patients prior to myocardial perfusion imaging. Only NT-proBNP proved significantly diagnostic, a cut off-concentration <25 ng/l predicting a normal perfusion scan with a negative predictive value >95%.[6] Similarly, in an angiographic study of 848 men and women with clinically suspected coronary artery disease, NT-proBNP performed better than hsCRP and ¤-glutamyltransferase, showing significant association with 3 vessel coronary artery disease, but it did not add to the predictive value of traditional cardiovascular risk factors. The authors were forced to conclude that it was of limited incremental value as a diagnostic tool.[7] The prognostic application of circulating biomarkers in stable coronary artery disease has also been disappointing. In a meta-analysis of 83 prospective studies reporting the association of CRP with death and nonfatal cardiovascular events, the authors found that the quality of the studies was so poor (only two reported a measure of discrimination) with evidence of reporting bias and publication bias that they were unable to make clinical practice recommendations.[8] Nevertheless, the data suggested that CRP measurements are unlikely to add anything to the prognostic discrimination achieved by considering blood pressure and other clinical factors in this patient group. In another study it was concluded that conventional clinical information provided an effective means of risk stratifying patients with stable coronary disease awaiting coronary bypass surgery and that additional prognostic information from CRP, measured singly or in combination with other biomarkers, was unlikely to be cost-effective.[9]

Medical treatment of angina

The medical treatment of angina has been the subject of renewed interest, not only because of the availability of novel therapies such as ivabradine and ranolazine, but also because of the recognition that it can compete favourably with revascularisation in many patients, both for controlling symptoms and for improving prognosis. Thus, COURAGE showed that in patients receiving optimal medical therapy (aspirin, beta-blocker and statin, plus ACE-inhibitor as indicated), percutaneous intervention (PCI) does not improve cardiovascular outcomes and incremental benefits in quality of life disappear by 36 months.[10,11] More recent meta-analyses of trials that have randomized patients with stable angina to PCI or medical therapy have come to similar conclusions.[12,13] This has led guideline groups to recommend optimal medical therapy, for the initial management of stable angina, with revascularisation reserved principally for patients whose symptoms are not satisfactorily controlled.[14]

Prognosis of angina

From the early Framingham finding that angina has "a mortality surprisingly close to that which follows the post-hospital phase of myocardial infarction"[15] to the trialists assertions that "cardiovascular risk (is) reduced to normal levels with contemporary therapy",[16] we now appear to have gone full circle with two recent outcome studies for patients with angina. The first included 1609 adults with ischaemic heart disease who were identified in primary care and were not, therefore, prone to the selection bias that affects secondary care cohorts.[17] The investigators found the hazards of all cause and coronary death in patients with angina alone compared with patients who had had previous myocardial infarction were 0.73 (95% CI 0.55 to 0.98) and 0.65 (0.44 to 0.98), respectively. Although statistically significant at the p <0.05 level these differences were not significant at the p <0.01 level suggested as appropriate for observational research. The investigators also found that physical functioning was consistently lower among those with angina alone. In the second study, the same group examined the prognosis of 1785 patients with angina as a first manifestation of ischaemic heart disease.[18] Within 5 years, 116 (6.5%) had an acute myocardial infarction, and 175 (9.8%) died. Male sex and each year of increasing age were both associated with increased hazard ratios for acute myocardial infarction (2.01 (1.35 - 2.97) and 1.04 (1.02 - 1.06), respectively) and all causes of mortality (1.82 (1.33 - 2.49) and 1.09 (1.07 - 1.11), respectively). An important finding was that an acute myocardial infarction after the index episode of angina greatly increased the risk of subsequent death. The authors concluded that appropriate control of risk factors and optimal use of preventive medical treatments should be aggressively pursued in patients with angina who represent a high risk group in primary care.

Interventional management of stable coronary artery disease

Clinical trials

Expectations that COURAGE would lead to changes in the management of stable angina, with renewed emphasis on optimal medical treatment (OMT) as the primary strategy,[19] have yet to be fulfilled, raising questions about how well informed patients are about the risks and benefits of PCI.[20] These questions have been amplified by recent studies showing that PCI is recommended over coronary artery bypass grafting (CABG) substantially more often than indicated by international guidelines, and fulfills the US societies' criteria for appropriateness in only 50.4% of cases.[21,22] Not only have rates of PCI in the US shown no tendency to decline since the publication of COURAGE[23] but a majority of patients are not being treated with OMT. In a large study of elective PCI procedures, rates of OMT

were only 43.5% in the 19 months before publication of COURAGE and 44.7%, in the 24 months afterwards, confirming that COURAGE has not yet had a palpable effect on interventional practice.[24]

Notable among recent reports from other PCI trials are the 10 year follow-up data from MASS II and the results of the STICH trial. MASS II randomized 611 patients with angina, multivessel coronary artery disease and preserved LV function to initial strategies of medical therapy or PCI or CABG.[25] The study was under-powered for the primary end-point of total mortality, Q-wave myocardial infarction, or refractory angina needing revascularisation, which occurred less frequently in the CABG group than in the PCI and medical therapy groups (33%, 42% and 59%, respectively). MASS II excluded patients with significant left main stem disease and total mortality was similar in all 3 groups. Nevertheless, the findings bear comparison with those reported in the early randomized trials of CABG *vs.* medical therapy[26] where patients with multivessel disease who were randomized to CABG survived longer than those randomized to medical therapy. STICH, however, has raised some doubt about the contemporary validity of those early randomized trials. In STICH 1212 patients with multivessel disease and severe left ventricular dysfunction (ejection fraction <35%) were randomized to coronary artery bypass surgery or medical therapy, to test whether surgical revascularisation would improve survival in this high risk group with ischaemic left ventricular dysfunction.[27] After nearly 5 years' follow-up all cause mortality (the primary endpoint) was similar between the groups, both in the main trial cohort and in a subgroup with demonstrable myocardial viability.[28] STICH confirms earlier reports[29] that the benefits of revascularisation in patients with ischaemic cardiomyopathy may have been exaggerated, even in patients with demonstrable viability. As the editorialist commented, contemporary medical therapy should not be under-estimated in the management of severe coronary artery disease.[30]

Meanwhile, further trials of PCI *vs.* CABG in selected groups with left main stem disease have been consistent in favouring CABG, based almost exclusively on lower rates of repeat revasularisation compared with PCI.[31-33] None of these trials showed significant mortality differences between the two revascularisation strategies, making PCI an option for those patients unwilling to undergo surgery and prepared to accept further interventional procedures as necessary. The SYNTAX trial has already identified PCI as a reasonable strategy for symptomatic multivessel disease, particularly if the SYNTAX score is low (≤22) when cardiovascular endpoints at 3 years are comparable to CABG, and this is reinforced by comparable quality of life outcomes.[34-36] More recently a pre-specified subgroup analysis of the ARTS-II registry has reported comparable outcomes for patients with multivessel disease involving the proximal LAD treated with either sirolimus-eluting stents or CABG.[37] These comparisons of PCI versus CABG in high risk disease, and medical therapy versus CABG in ischaemic cardiomyopathy begin to erode confidence in the long-held view that surgery is the most appropriate treatment option in such patients.

Procedural factors

Radial versus femoral access. Debate about the merits of radial versus femoral access for interventional procedures has not been resolved by RIVAL, the first comparative study powered for cardiovascular outcomes.[38] Among 7021 patients with ACS undergoing cardiac catheterization with a view to intervention, the primary outcome (a composite of death, myocardial infarction, stroke or non-CABG-related bleeding at 30 days) occurred in similar proportions of radial (3.7%) and femoral (4.0%) access groups. The marginal difference in favor of radial access was driven by a trend towards lower bleeding rates at 30 days (0.7% *vs.* 0.9%), associated with significantly lower rates of access site complications including large haematomas and pseudoaneurysms. Smaller studies[39] have reported less bleeding with radial access which, coupled with earlier mobilization, has encouraged its adoption in many European centers. Femoral access, however, is still preferred by many operators because access is more predictable, procedure times may be shorter and radiation exposure lower compared with the radial approach.[40,41] Ultimately, it seems, institutional experience is a major determinant of procedural success, high volume radial centres in RIVAL recording the lowest hazard of the primary outcome.

Pressure wire. Pressure wire measurement of fractional flow reserve (FFR) is now widely used by interventionists for per-procedural assessment of the functional significance of coronary stenoses. In the FAME study 1005 patients with multivessel coronary artery disease undergoing DES implantation were randomized to procedures guided by angiography alone or by angiography plus FFR measurement, values <0.80 providing indication for stenting.[42] In the FFR group, the number of stents per patient (1.9 ± 1.3 *vs.* 2.7 ± 1.2) and the primary endpoint of death, nonfatal myocardial infarction or target vessel revascularisation at 1 year (13.2% *vs.* 18.3%) were both significantly lower compared with the angiography group. Benefits were largely sustained at two years[43] and evidence of cost-effectiveness[44] completes the case in favour of FFR-guided PCI in multivessel procedures.

Bifurcation PCI. Debate surrounding bifurcation PCI has been largely resolved by studies showing that simple stenting of the main branch - with "provisional" stenting of the side branch only if flow becomes compromised - is superior to strategies that involve complex stenting of both limbs of the bifurcation. A recent meta-analysis of randomized trials has confirmed superiority of the simple stenting strategy which yields better results in terms of in-hospital and late myocardial infarction with similar rates of restenosis and target vessel revascularisation compared with the complex strategy.[45] Further refinement of the simple stenting strategy has now been tested by randomising 477 patients either to final kissing balloon inflation or to no-final kissing balloon inflation.[46] Final kissing balloon inflation was associated with a significantly lower rate of angiographic side branch restenosis (8% *vs.* 15%) at 6 months compared with no-final kissing balloon inflation, although rates of the primary endpoint -cardiac death, myocardial infarction, stent thrombosis, or target-lesion revascularization- were similar (2.1% *vs.* 2.5%). The data therefore do not provide a compelling argument for final

kissing balloon inflation after simple birfurcation stenting although the strategy does seem to provide some protection against side branch restenosis.

LV support devices. Intra-aortic balloon pump (IABP) support in high risk PCI is widely recommended, but a recent randomized trial in 301 patients with severe LV dysfunction (ejection fraction ≤30%) and advanced coronary artery disease found no evidence of benefit.[47] Rates of in-hospital major adverse cardiac events were similar with (15.2%) or without (16.0%) the IABP, arguing against its elective use in this group of patients. Alternative methods of circulatory support during PCI are now being investigated and registry data for the Impella 2.5 percutaneous LV assist device (LVAD) confirm that it can be safely positioned across the aortic valve from the femoral approach and supply flow rates of up to 2.5L/min during interventional procedures.[48] These promising data distinguish the Impella from most other LVADs, which require surgical deployment and have no role in the catheter laboratory.[49]

Acute kidney injury (AKI). Contrast induced AKI is a well-recognized complication of angiographic procedures and a recent Canadian study shows that it has important association with adverse long term outcomes.[50] Among 14782 adults undergoing cardiac catheterization, the adjusted risk of death during a median 19.7 months follow-up increased progressively with the post-procedural severity of AKI, patients with stage 2 or 3 AKI during the first 7 days after catheterization having nearly 4 times the hazard of death compared with no AKI. Risks of subsequent hospitalizations for heart failure also increased. Interestingly, AKI has been reported less commonly with catheterisation using the radial approach compared with the femoral approach.[51] Pre-hydration may be protective in high-risk individuals, particularly people with diabetes, but no other specific treatments have shown unequivocal benefit.

Bleeding. Peri-procedural bleeding, associated with adverse outcomes after PCI, has shown notable declines in recent years.[52] Radial access has likely contributed (see above) but other bleeding avoidance strategies have been emphasised in a study of 1,522,935 patients entered in the National Cardiovascular Data Registry (NCDR) CathPCI Registry.[53] The study showed that vascular closure devices and bivalirudin therapy together were associated with a reduction of bleeding events from 2.8% to 0.9%, yet these strategies were used least often in patients with a high pre-procedural risk of bleeding assessed with the NCDR bleeding risk model.[54] Based on these findings it seems clear there remains considerable scope for improving the safety of PCI by pre-procedural identification of patients with most to gain from individualized bleeding avoidance strategies.

Myocardial injury. Myocardial injury during PCI is common and a recent meta-analysis of 15 studies embracing 7578 patients found troponin elevation in 28.7% of procedures.[55] Any level of raised troponin was associated with an increased risk of cardiovascular events and for those with myocardial infarction according to the universal definition[56] the odds ratio for MACE at 18 months was 2.25 (1.26 – 4.00). Direct evidence of peri-procedural myocardial injury has now been made available from CMR imaging which documented new myocardial hyperenhancement (median mass 5.0 g) in 32% of 152 patients undergoing PCI. After adjustment for age and sex, these patients had a 3.1-fold (95% confidence interval 1.4 to 6.8; $p = 0.004$) higher risk of adverse outcome than patients without new hyper-enhancement.[57] These data have enhanced interest in pharmacological and mechanical interventions directed at protecting the myocardium during elective PCI. High dose statins show promise in this regard, and in one study of 668 stain-naïve patients, periprocedural myocardial infarction (defined as a CK-MB elevation >3x ULN) occurred in 9.5% of those randomized to a single loading dose of atorvastatin 80mg, compared with 15.8% in the control group.[58] Most patients should already be taking statins prior to elective PCI but for those who are not, these data indicate that pre-procedural loading along with aspirin and clopidogrel is a potential means of enhancing patient safety. Also promising is remote ischaemic preconditioning which in a recent randomized trial of 242 patients undergoing elective PCI was associated with reduced troponin I release at 24 hours compared with controls (0.06 *vs*. 0.16 ng/mL; $p = 0.040$).[59] The major adverse cardiac and cerebral event rate at 6 months was also lower in the remote ischaemic preconditioning group (*4 vs*. 13 events; $p = 0.018$). However, this was a small unblinded trial and further research is needed before this inexpensive means of myocardial protection can be recommended in routine clinical practice.

Percutaneous intervention in special groups

Prior radiotherapy Thoracic radiotherapy in women with breast cancer increases the long-term risk of cardiovascular death,[60] possibly by induction of a sustained inflammatory response in irradiated arteries.[61] It is also associated with adverse outcomes for coronary stenting, with a hazard ratio for all cause death after 6 years of 4.2 (95% CI 1.8 to 9.5) compared with people who have not undergone radiotherapy.[62]

Diabetes. CABG has long been the preferred revascularisation strategy in patients with diabetes and multivessel disease, and the publication of BARI-2D and CARDIA has done little to challenge this orthodoxy. In BARI-2D, 2368 patients with type 2 diabetes (31% with three vessel disease) were stratified as being appropriate for either PCI or CABG and then randomized to contemporary medical treatment or revascularization.[63] After follow-up for an average of 5.3 years, rates of all-cause mortality (the primary end-point) were similar for the medical and revascularisation groups, but in the CABG stratum patients assigned to revascularization had lower cardiovascular event rates (death, MI or stroke) than patients assigned to medical therapy. However, the patients in BARI-2D randomized to revascularisation obtained greater symptomatic benefit than the medically treated group.[64] In CARDIA, 510 patients with diabetes, 93% of whom had multi-vessel disease, were randomized to PCI or CABG.[65] The composite rate of all-cause mortality, nonfatal MI, and nonfatal stroke at 1 year, was 13.0% for PCI and 10.5% for CABG; this difference was not statistically significant but the study was under-powered and non-inferiority for PCI compared with CABG was not confirmed. It is the BARI-2D

findings, therefore, that generated greater interest by showing that contemporary medical treatment of diabetic patients with complex coronary artery disease compares favourably with revascularisation.

Outcomes for percutaneous coronary intervention

Outcomes for PCI (and for CABG) continue to improve.[66] Pre-procedural risk factors for adverse outcomes are well defined and include impaired LV function, complex lesion morphology, emergency procedures, and diabetes. To this list may now be added the Euroscore which showed excellent discrimination for predicting hospital mortality (area under the ROC curve 0.91 (95% CI 0.86 to 0.97)) in 1173 PCI patients, with the odds of death increasing as the score rose.[67] The Euroscore is already validated and widely used to predict surgical risk and the authors suggest that it is therefore well placed to help cardiologists and cardiac surgeons individualize the risk profile of patients in order to better select the appropriate revascularisation strategy. External validation of the Euroscore in other PCI cohorts is now needed before its clinical application can be confidently recommended. Meanwhile the SYNTAX score, based on specific anatomic characteristics of the coronary angiogram, remains the best validated means of anticipating the risks of PCI and CABG, although its value for predicting 12 month outcomes is confined to PCI.[68]

Second Generation Drug Eluting Stents

Drug eluting stents (DES) have produced important reductions in rates of restenosis compared with bare metal stents (BMS), albeit at increased risk of late stent thrombosis.[69] This has provided impetus for the design of more effective "second-generation" drug eluting stents that have been the subject of investigation in 4 recent trials all of which were powered for clinical events with a primary composite endpoint of cardiac death, myocardial infarction, or target-vessel revascularization. The largest of these, SPIRIT IV, randomized 3687 patients in a 2:1 ratio to receive second-generation everolimus-eluting stents (EES) or first-generation paclitaxel-eluting stents (PES).[70] The study confirmed superiority of EES over PES not only in terms of the composite clinical endpoint (4.2% *vs.* 6.8%), but also in terms of stent thrombosis (0.2% *vs.* 0.8%). The single centre COMPARE Trial compared second generation EES with second-generation PES in 1800 patients and again showed superiority of the EES, which at 12 months was associated with a 6% incidence of the primary endpoint compared with 9% in the PES group.[71] The second generation zotarolimus-eluting stent (ZES) has been evaluated against sirolimus-eluting (SORT OUT III, n=2332) and everolimus-eluting stents (Resolute All Comers Trial, n = 2292). In SORT OUT III, ZES proved inferior to SES, with primary endpoint rates of 6% *vs.* 3%, a difference sustained at 18 months.[72] In Resolute All Comers the composite clinical endpoint at 1 year occurred in almost identical (8.2% and 8.3%) proportions of ZES and EES groups, but the ZES group showed a trend for more frequent stent thrombosis (2.3% *vs.* 1.5%) and greater in-stent late lumen loss (0.27 mm *vs.* 0.19 mm). These observations raise further concerns about zotarolimus-eluting stents that will not be resolved until the 5 year follow-up data become available.[73] Long-term results of zotarolimus-eluting stents have been favourable in registries,[74] but the results of these 4 randomised trials have ensured that second generation everolimus-eluting stents are now the first choice for most interventionists.

Moving beyond the second generation of drug eluting stents, polymer-free and biodegradable polymer drug-eluting stents are now entering the clinical arena. A randomized comparison of rapamycin delivery using these novel platforms versus conventional (permanent) polymer coated sirolimus eluting stents, showed comparable safety and comparable efficacy for prevention of clinical restenosis during the two year follow-up. However, angiographic surveillance confirmed more sustained neointimal suppression with the polymer-free rapamycin eluting stent compared with the other platforms.[75] Everolimus delivery by a bioabsorbable stent in 30 patients also produced impressive 2 year outcomes with no cardiac deaths, ischaemia-driven target lesion revascularisations, or stent thromboses recorded.[76] Interestingly, vasomotion was restored in the stented segment after bioabsorption. These results will doubtless ensure continuing interest in the development of polymer-free drug eluting stents.

Bare metal stents

The advantages offered by drug eluting stents in management of coronary artery disease have seen continuing indications for bare metal stents (BMS) diminish almost to the point of extinction. The superiority of DES compared with BMS for primary PCI is driven by significantly lower rates of target lesion revascularisation and recent data show the benefit is sustained after 3 years (9.4% *vs.* 15.1%) with no significant differences in the rates of death, reinfarction, or stent thrombosis.[77] Current recommendations are for the preferential use of DES in ST elevation myocardial infarction, particularly in patients with high-risk features for restenosis such as long lesions, small vessels, or diabetes.[78] The BASKET-PROVE study now also challenges the notion that bare metal stents have residual indications in large coronary arteries.[79] These investigators randomized 2314 patients requiring 3 mm to 4 mm diameter coronary stents to receive first-generation sirolimus-eluting stents (SES), second-generation everolimus-eluting stents (EES), or cobalt-chromium BMS. After 2 years cardiovascular event rates and rates of stent thrombosis were comparable between the 3 groups, but the rates of clinically driven TVR were only 4.3% with SES and 3.7% with EES compared with 10.3% with BMS. Although cost-effectiveness was not reported these findings confirm that the benefits of DES in terms of safety and protection against restenosis in small coronary arteries extend to procedures undertaken in larger vessels.

Paclitaxel-coated balloon

PCI in very small vessels (<3mm) remains a challenge. Use of DES has improved safety and longer-term outcomes relative to BMS,[80] and in a randomized trial proved superior

to the newly available paclitaxel-coated balloon in terms of restenosis after 6 months.[81] Nevertheless, a potentially important coronary application of the paclitaxel-coated balloon for treatment of in-stent restenosis has now been identified, a recent randomised trial in 131 patients with bare metal in-stent restenosis reporting 6 month binary restenosis rates of only 7% for the drug coated balloon compared with 20% for a paclitaxel-eluting stent.[82] However, longer-term data will be needed, a recent registry study reporting that sirolimus-eluting stents used for treatment of bare metal in-stent restenosis exhibit sustained efficacy at 4 years with a target lesion revascularisation rate of only 11.1%.[83]

Antiplatelet therapy

Stent thrombosis. Dual antiplatelet therapy with aspirin and clopidogrel (DAPT) is considered an essential adjunct to PCI to protect against stent thrombosis. Guidelines recommend DAPT to continue for 12 months in patients who have received drug-eluting stents to allow for complete endothelialisation of the struts, whereupon treatment can continue with aspirin alone. However, very late stent thrombosis remains a real concern and has received attention in a number of recent studies either by evaluating the potential benefits of prolonging DAPT beyond 12 months or by up-titrating antiplatelet therapy against the results of platelet function tests. The impact of prolonged DAPT beyond 12 months has been evaluated in a registry study, which found no additional protection against death or MI compared with DAPT for ≤12 months.[84] This was confirmed in a randomised trial of continuing aspirin and clopidogrel versus monotherapy with aspirin in 2701 patients who had already received DAPT for 12 months after PCI.[85] At two years' follow-up, rates of myocardial infarction and death were similar in the two groups (1.8% *vs.* 1.2%), providing support for the guideline recommendation to continue DAPT for 12 months after PCI with drug eluting stents. However, the importance of strict adherence to DAPT in the first 12 months is emphasised by the finding in another recent study that patients who delayed filling their prescription for clopidogrel after hospital discharge had almost twice the risk of myocardial infarction or death compared with those who filled their prescription on the day of discharge, even though the median delay was only 3 days.[86]

High residual platelet reactivity. An alternative approach for protecting against stent thrombosis is to target more aggressive treatment at patients with high residual platelet reactivity after clopidogrel loading. Such patients appear to be at significantly increased risk of adverse events, and in a recent study of 215 patients undergoing unprotected left main stem PCI the risk of cardiac death at 1 year was more than doubled in those with high residual platelet activity.[87] The GRAVITAS Investigators have now reported their randomized comparison of standard dose (75 mg) *vs.* high dose (150 mg) clopidogrel after drug-eluting stenting in 2214 patients with high on-treatment platelet reactivity.[88] Although high dose clopidogrel was effective in reducing platelet reactivity, cardiovascular event rates (death, myocardial infarction, stent thrombosis) after 6 months were identical at 2.3% in both groups. The failure of aggressive antiplatelet treatment to reduce event rates in patients with high residual platelet reactivity was, perhaps, surprising but will not be the last word on this subject, as other such studies are in progress. Meanwhile calls for platelet reactivity monitoring in patients receiving clopidogrel seem premature.[89]

A potential mechanism of high residual platelet reactivity in some patients treated with clopidogrel relates to conversion of the pro-drug to an active metabolite by the hepatic cytochrome P-450 system. Conversion is genetically determined and is reduced in carriers of common loss-of-function CYP alleles, who show decreased platelet inhibition and a 1.53 to 3.69 increased risk of cardiovascular events compared with non-carriers.[90-92] This led to calls for higher clopidogrel dosing in carriers of the loss-of-function alleles but this policy has now been questioned by a study that stratified patients enrolled in two large randomized trials of clopidogrel therapy by genotype status.[93] In neither trial did loss-of-function carrier status affect the primary composite efficacy outcomes, or safety outcomes with respect to bleeding. The authors concluded that carriers of loss-of-function CYP alleles should receive clopidogrel at currently recommended doses in acute coronary syndromes, although for atrial fibrillation the conclusion was qualified by a need for larger studies. Meanwhile genotyping of patients with acute coronary syndromes enrolled in a head-to-head comparison of clopidogrel with ticagrelor (PLATO) reported that the hazard of the primary endpoint was lower for patients randomized to ticagrelor compared with clopidogrel but relative risk reduction was unaffected by CYP or ABCB1 (coding for a protein influencing clopidogrel absorption) genotype.[94] On present evidence, therefore, genetic testing does not appear to be helpful in determining clopidogrel's effectiveness in comparison with placebo or ticagrelor and is unlikely to provide a useful basis for determining dosing strategies.

Drug interaction. Another potential mechanism of high residual platelet reactivity in some patients receiving platelet inhibitors is an interaction with some proton pump inhibitors (PPIs), which may reduce clopidogrel's conversion to its active metabolite by interfering with the hepatic cytochrome P-450 system and may also reduce the platelet response to aspirin.[95] However, in a large cohort study event rates among patients discharged on PPIs were increased independently of whether or not they were also discharged on clopidogrel, indicating that drug interaction was not the responsible mechanism.[96] Moreover, the COGENT trial of 3873 patients receiving DAPT and randomized to omeprazole or placebo was reassuring in showing no difference in the primary cardiovascular end point, a composite of death from cardiovascular causes, nonfatal myocardial infarction, revascularization, or stroke.[97] COGENT found that patients randomized to omeprazole had a significantly lower rate of gastrointestinal bleeding and, given the gastro-protective effects of PPIs in patients on low-dose aspirin, recently confirmed in the OBERON trial,[98] the benefits seem to outweigh any potential risk related to clopidogrel interaction. Other drugs that have come under recent scrutiny include calcium channel blockers (CCBs) which, like PPIs, are metabolized by the hepatic cytochrome P-450 system and have the

potential therefore to interact with clopidogrel. Observational data in patients taking clopidogrel have shown that high residual platelet reactivity is more common in those co-prescribed CCBs than in those who are not,[99] and an earlier observational study reported that this may be associated with a higher cardiovascular event rate 2 years after PCI.[100] Interpretation of these studies needs to be cautious however and more prospective data are needed, ideally in the form of randomized trials.

Coronary Artery Bypass Surgery in Stable Coronary Disease

Among key technical innovations of the last 15 years has been off-pump CABG but its potential benefits in terms of myocardial and cerebral protection have had to be weighed against problems of incomplete revascularisation and reports of an increased risk of myocardial infarction and early graft attrition compared with on-pump procedures. Two randomized trials have now clarified some of these issues. The ROOBY investigators randomized 2203 patients to on-pump or off-pump CABG and found no significant difference in rates of the 30 day composite outcome (7.0% *vs.* 5.6%, respectively for death, reoperation, new mechanical support, cardiac arrest, coma, stroke, or renal failure).[101] After 1 year the same composite was higher for off-pump than for on-pump CABG (9.9% *vs.* 7.4%, $p = 0.04$) and graft patency was lower (82.6% *vs.* 87.8%, $p < 0.01$) in the 1371 patients who had follow-up angiography. Meanwhile a careful assessment of 12 month cognitive outcomes found no difference between the groups although the rate of impairment by either procedure was reassuringly low.[102] Shortly after the ROOBY report, the "Best Bypass Surgery" trialists published their results in a higher risk group (Euroscore ≥5, 3-vessel disease) of 341 patients randomized to on-pump or off-pump CABG.[103] Again, the composite primary outcome (all-cause mortality, acute myocardial infarction, cardiac arrest with successful resuscitation, low cardiac output syndrome/cardiogenic shock, stroke, and coronary reintervention) was similar for the on-pump and off-pump groups (15% and 17%; $p = 0.48$) and after 3 years all-cause mortality was significantly increased in the off-pump group (24% *vs.* 15%; HR 1.66, 95% CI 1.02 to 2.73; $p = 0.04$).[104] These trials have not provided evidence of clinical superiority for off-pump CABG although it is premature to consider abandoning the procedure. Conventional cardiopulmonary bypass has important deleterious effects that include platelet and neutrophil activation, consumption of coagulation factors, complement generation and the release of pro-inflammatory mediators with generation of a systemic inflammatory response. If off-pump surgery cannot deliver better clinical outcomes it may be prudent to take heed of the editorialist and consider "better-bypass" in the form of a miniaturized bypass system.[105] This was the subject of a recent meta-analysis which found that miniaturized cardiopulmonary bypass when compared with conventional cardiopulmonary bypass was associated with a somewhat lower rate of death (1.1% *vs.* 2.2%, OR 0.58, 95% CI 0.23 to 1.47, $p = 0.25$) and stroke (0.2% *vs.* 2.0%, OR 0.25, 95% CI 0.06 to 1.00, $p = 0.05$) in the immediate post-operative period (106). Now needed are larger trials to further evaluate miniaturized cardiopulmonary bypass.

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