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Abbreviations used in this issue:

CV = cardiovascular; DAPT = dual antiplatelet therapy; DES = drug-eluting stent; FFR = fractional flow reserve; iFR = instantaneous wave-free ratio; LAD = left anterior descending; MI = myocardial infarction; STEMI = ST-segment elevation MI; PCI = percutaneous coronary intervention; TVR = target-vessel revascularisation.

Welcome to issue 24 of Interventional Cardiology Research Review.

Research selected for this issue includes a UK study reporting similar FFR (fractional flow reserve) values when adenosine was infused into a vein in the hand rather than the femoral vein, which has important implications in the transradial era. Other researchers have presented real-world data suggesting that despite comparable reperfusion rates between nonagenarians and younger patients with acute MI undergoing primary PCI, nonagenarians had much greater hospital mortality. Data were reported supporting the use of the iFR (instantaneous wave-free ratio) for establishing the functional significance of coronary stenoses, particularly when used in a hybrid approach with FFR. A placebo-controlled trial published in N Engl J Med found that pre-PCI intravenous cyclosporin did not attenuate reperfusion injury or reduce infarct size in patients with acute MI.

I hope you enjoy the research selected, and I look forward to receiving your comments, feedback and suggestions.

Kind Regards,

Associate Professor Craig Juergens
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Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation

Authors: Fiedler KA et al.

Summary: Patients receiving concomitant aspirin and oral anticoagulation and who had undergone DES implantation were randomised to receive 6 weeks (n=307) or 6 months (n=307) of clopidogrel. There was no significant difference between the 6-week and 6-month clopidogrel arms for rates of the primary composite endpoint (death, MI, definite stent thrombosis, stroke, TIMI (thrombolysis in MI) major bleeding at 9 months; 9.8% vs. 8.8% [p=0.63]), the secondary ischaemic endpoint (cardiac death, MI, definite stent thrombosis, ischaemic stroke; 4.0% vs. 4.3% [p=0.87]) or the secondary bleeding endpoint (TIMI major bleeding; 5.3% vs. 4.0% [p=0.44]).

Comment: Patients with an indication for oral anticoagulation who undergo stenting are faced with the prospect of triple therapy with the addition of DAPT. To date there has only been one randomised trial to help guide which agents and for how long. This open-label study represents the second randomised controlled trial and adds to the discussion suggesting that in the context of DES use, 6 weeks of triple therapy was not superior to 6 months of therapy with respect to ischaemic or bleeding events. The overall rate of stent thrombosis was low (0.7% vs. 0.0% in the two groups) in this predominantly stable angina population (>66% in each group). We await larger studies that will address the use of novel oral anticoagulants, but it seems shortening the duration of triple therapy, balancing ischaemic and bleeding risk, to 6 weeks seems a reasonable place to start.

Reference: J Am Coll Cardiol 2015;65(16):1619–29

Abstract

Independent commentary by Associate Professor Craig Juergens

Independent Cardiologist and Head of Cardiology, Liverpool Hospital, Sydney.
Fractional flow reserve in the transradial era: will hand vein adenosine infusion suffice?

Authors: Scott P et al.

Summary: This study compared the extent, rapidity and stability of hyperaemia for intravenous infusions of adenosine 140 µg/kg/min via a 20-gauge cannula in the back of the hand versus a 5 or 6Fr femoral venous sheath to achieve peak hyperaemia during FFR. Sixty-one patients presenting for coronary angiography/intervention and requiring a pressure-wire study were recruited and received adenosine infusions sequentially via both routes with a washout period in between. The mean FFR measured using adenosine in both routes was 0.85. Compared with femoral adenosine administration, administration into the hand was associated with a significantly longer time to peak hyperaemia (63 vs. 43 sec [p<0.0001]), with no significant difference in FFR stability (p=0.43).

Comment: FFR has become an important tool to help guide coronary intervention. To ensure accuracy, maximal hyperaemia using adenosine is necessary and it has been traditionally suggested that this be given by infusion via a central venous line. With the rise in radial intervention, it is not convenient to quickly access the femoral vein if a large bore antecubital vein is not already in situ. This interesting small single-centre study demonstrated that an infusion of adenosine through a 20-gauge (pink) cannula in the hand produced FFR values very similar to that produced by a 5 or 6Fr femoral sheath, although the time to maximal hyperaemia was longer. This simply means we need to wait an average of 22 seconds longer, which is not likely to be clinically relevant compared with the time taken and potential morbidity of gaining femoral venous access.


Intermediate outcomes in the prospective, multicenter Coarctation of the Aorta Stent Trial (COAST)

Authors: Meadows J et al., on behalf of the COAST Investigators

Summary: This paper reported 2-year results of the COAST trial, which assessed a platinum-iridium stent (Cheatham Platinum) in 105 children and adults with native or recurrent coarctation; stent implantation was successful in all but one participant, with no procedural deaths, serious adverse events or surgical intervention needed. The immediate reductions in upper- to lower-extremity blood pressure differences were sustained out to 2 years, as were 12-month decreases in hypertension and medication use rates. Of six aortic aneurysms that occurred, five were successfully treated with covered stent placement and the other resolved without intervention. Two patients had stent fractures at 1 year, and this had increased to 11 patients at 2 years with evidence of fracture progression and an association with larger stent diameter. Twelve additional stent fractures occurred after 2 years. However, no stent fracture led to loss of stent integrity, stent embolisation, aortic wall injury or reobstruction. There were nine reinterventions associated with stent redilation and aneurysms during the first 2 years and ten more after 2 years.

Comment: Coarctation of the thoracic aorta is a relatively common form of congenital CV disease and endovascular treatment is often preferred over surgery despite the lack of a US FDA approved device for this indication. This study presents follow-up data on the performance of this platinum-iridium alloy stent. Notably, the stent was only deployed if predilatation demonstrated compliance of the aorta through the lack of a significant waist. Reintervention was relatively common, but this is often planned as patients grow older and the stent needs further dilatation. The high number of stent fractures, although not resulting in sequelae, and the six aneurysms that needed treatment are of some concern, but this should be balanced with the potential morbidity of surgery in this young patient cohort.


Heart Failure Research Review


www.researchreview.com.au
Outcomes of primary percutaneous coronary interventions in nonagenarians with acute myocardial infarction

Authors: Heff G et al.

Summary: This analysis of 26,157 registry patients who underwent primary PCI compared demographics, procedural and in-hospital outcomes between those aged ≥90 (n=418) vs. <90 years. Compared with the younger patients, the nonagenarians were more likely to be female (62.3% vs. 22.5% [p<0.001]), be non-smokers (81.6% vs. 36.7% [p<0.001]), be in cardiogenic shock at admission (10.5% vs. 4.8% [p<0.001]) and to have significant comorbidities. The nonagenarians were less likely to undergo PCI via the radial artery than the younger patients (61% vs. 72.1% [p=0.007]) and undergo DES implantation (4.4% vs. 16.7% [p<0.001]), but their in-hospital mortality rate was greater (24.9% vs. 5.1%; adjusted odds ratio 4.31 [95% CI 3.26–5.71]), despite no significant difference in PCI success rate (96.1% vs. 98.7% [p=0.33]).

Comment: Advanced age is a strong predictor of adverse outcomes in the setting of STEMI, but few data exist of the outcome of primary PCI in patients aged >90 years of age. This registry study from Paris compared the outcomes of ≥90 (1.6% of total) of these patients. Notably these patients presented later and took longer to get to the cath lab, but impressively 61.1% of patients had radial access. In-hospital mortality was very high and was not entirely accounted for by a higher incidence of multivessel and left-main disease, or presenting in shock, suggesting the extreme age was a factor. Although I suspect this was a highly selected cohort of nonagenarians, the results are informative as the alternatives of thrombolysis or conservative treatments are likely to result in even higher morbidity and mortality.

Reference: Int J Cardiol 2015;189:24–9

Abstract

Angiographic characteristics of intermediate stenosis of the left anterior descending artery for determination of lesion significance as identified by fractional flow reserve

Authors: Biasio L et al.

Summary: These researchers analysed 1883 lesions on coronary angiograms from a retrospective cohort of 1350 patients for stenosis grade, matched with FFR values, to investigate if more comprehensive evaluation may help identify flow-limiting stenoses. Angiography-derived optimal cutoff values for delineating the 90% sensitivity, 90% specificity range were 50.8% for the left main artery, 62.2% for the proximal/mid LAD (left anterior descending) artery, 66.3% for the proximal/mid right coronary artery. 70.5% for the proximal left circumflex/first obtuse marginal segment and 71.4% for more distal segments. Among patients with intermediate lesions in the LAD artery, the following five angiographic parameters were independent predictors of flow limitation: i) a 30–50% lesion proximal to the lesion of interest; ii) lesion length >20mm; iii) distal take-off of all diagonal branches ≥2mm diameter; iv) ‘apical wrap’ of the LAD artery; and v) collaterals to an occluded left circumflex/right coronary artery. A risk score for predicting flow limitation in intermediate lesions in the LAD artery was derived from these findings.

Comment: FFR has become the gold standard for the assessment of functionally significant coronary stenosis, but requires infusion of adenosine and placement of a wire driven pressure transducer. In practice, most operators still use visual estimation of the coronary lesion to decide on treatment strategies. This study attempted to develop a risk score for predicting a functionally significant lesion using angiographic parameters. The features identified make intuitive sense, but need to be validated prospectively, which appears to be the authors’ plan.


Abstract

Benefits and risks of extended duration dual antiplatelet therapy after PCI in patients with and without acute myocardial infarction

Authors: Yeh RW et al.

Summary: Patients undergoing coronary stent implantation (n=11,684, including 9961 treated with DESs and 1687 with bare-metal stents) received 30 months or 12 months of postprocedural DAPT in the placebo-controlled Dual Antiplatelet Therapy Study; this research compared benefits and risks in participants with (30.7%) versus without MI on presentation. Compared with placebo, continued thienopyridine therapy was associated with less stent thrombosis between 12 and 30 months in participants with and without MI (0.5% vs. 1.9% [p<0.001] and 0.4% vs. 1.1% [p<0.001], respectively; p=0.69 for interaction), whereas a significant reduction in major adverse CV and cerebrovascular events with continued thienopyridine was seen in patients with MI at presentation (3.9% vs. 6.8% [p<0.001]), but not in those without MI at presentation (4.4% vs. 5.3% [p=0.08]; p=0.03 for interaction). Continued thienopyridine reduced subsequent MI in both the respective groups with and without MI at presentation (2.2% vs. 5.2% [p<0.001] and 2.1% vs. 3.5% [p<0.001]; p=0.15 for interaction) but increased bleeding (1.9% vs. 0.8% [p=0.005] and 2.6% vs. 1.7% [p=0.007]; p=0.21 for interaction).

Comment: The multinational, multicentre Dual Antiplatelet Therapy Study showed that prolonging DAPT to 30 months as opposed to 12 months after PCI resulted in reductions in stent thrombosis and MI with increased bleeding. This study looked at the 30.7% of patients in the DAPT population who had MI (47% STEM1 and stenting). The results were consistent with the entire cohort; however, the benefits with respect to reducing stent thrombosis and MI were greater in this cohort with a similar increased risk of bleeding. Interestingly, the absolute reduction in nonstenst thrombosis-related MI was 1.5% in the MI cohort and 0.6% in the no-MI cohort, accounting for only half the reduction in nonfatial MI in both groups, suggesting it is not ‘all about the stent’. As always the risk-benefit profile should be carefully considered in each patient to decide whether continuing DAPT beyond 1 year is prudent.

Reference: J Am Coll Cardiol 2015;65(20):2211–21

Abstract

Prospective assessment of the diagnostic accuracy of instantaneous wave-free ratio to assess coronary stenosis

Authors: Escaned J et al.

Summary: The ADVISE II study investigated limitations of previous iFR versus FFR comparisons for 690 intermediate coronary stenoses during baseline and hyperaemia from 598 patients. A prespecified iFR cutoff of 0.89 correctly classified 82.5% of stenoses with sensitivity and specificity values of 73.0% and 87.8%, respectively (C-statistic 0.90 [p<0.001]), and 91.6% of stenoses were correctly classified by an iFR outside of the prespecified treatment (≤0.85) and deferral (≥0.94) values. Combining FFR with iFR within these cutoffs, 94.2% of stenoses were correctly classified, and this approach avoided the need for vasodilators in 65.1% of patients and 63.1% of stenoses.

Comment: The iFR is a recently introduced pressure-derived index that does not rely upon maximal hyperaemia to assess the functional significance of coronary stenoses. This prospective, multiinstitutional study aimed to compare iFR with the gold standard of FFR. All pressure recordings were analysed by an independent core laboratory, and notably ~25% of the FFR measurements were excluded, suggesting great care must be exercised in using this technology. A so-called hybrid approach was used whereby an iFR <0.85 is considered significant, an iFR >0.94 is deemed non-significant, and patients with measurements in between are given intravenous adenosine and a formal FFR is measured. Utilising this approach, iFR properly classified 94% of lesions and obviated vasodilator use in 69% of cases, which potentially makes the procedure less uncomfortable for the patient. Future studies should look at clinical outcomes before it can replace FFR.


Abstract

A prospective randomized trial of drug-eluting balloons versus everolimus-eluting stents in patients with in-stent restenosis of drug-eluting stents

Authors: Alfonso F et al.

Summary: Patients with DES in-stent restenosis were randomised to receive a drug-eluting balloon (n=154) or an everolimus-eluting stent (n=155) in the RIBS IV trial. Compared with drug-eluting balloon recipients, everolimus-eluting stent recipients had, at late angiography in a median 247 days, a larger minimal lumen diameter (2.03 vs. 1.90mm [p<0.01]), greater net lumen gain (1.28 vs. 1.01mm [p<0.01]), lower percent diameter stenosis (23% vs. 30% [p<0.01]) and a lower binary restenosis rate (11% vs. 19% [p=0.06]); the results of an in-lesion analysis were similar. Everolimus-eluting stent recipients also had a lower event rate of the composite of cardiac death, MI and TVR at 1-year clinical follow-up than drug-eluting balloon recipients (10% vs. 18% [p=0.04]), due mainly to a lower TVR rate (8% vs. 16% [p=0.03]).

Comment: The use of DESs has greatly reduced restenosis, but in-stent restenosis still occurs and can be associated with poor outcomes, and it is unclear which is the optimal way of dealing with it. This prospective multicentre, open-labeled randomised controlled trial provides some insights as to the best approach. Notably, intracoronary imaging techniques were recommended as part of the protocol to assess underlying substrate and stent expansion. The investigators found treatment with a second-generation DES (Xience Prime) was superior to treatment with a paclitaxel-eluting balloon (SeQuent, B. Braun) and perhaps this should be the default strategy for a first episode of DES in-stent restenosis. Drug-eluting balloons may still have a role in patients with multiple layers of stent, with large side-branch involvement or perhaps where a shorter duration of DAPT is required, although these subgroups require more investigation.

Reference: J Am Coll Cardiol 2015;66(1):23–33

Abstract
Cyclosporine before PCI in patients with acute myocardial infarction

Authors: Cung T-T et al.

Summary: Patients with acute anterior STEMI scheduled for PCI within 12 hours of symptom onset and who had complete occlusion of the culprit coronary artery were randomly allocated to receive a bolus intravenous injection of cyclosporin 2.5 mg/kg (evaluable n=398) or placebo (evaluable n=390) before coronary recanalisations. There was no significant difference between cyclosporin and placebo recipients for the rate of the primary composite outcome of all-cause mortality, worsening heart failure during initial hospitalisation, rehospitalisation for heart failure or adverse left ventricular remodelling at 1 year (59.0% vs. 58.1% [p=0.77]), any of the individual component outcomes, recurrent infarction, unstable angina, stroke or safety profile.

Comment: Despite enormous progress developing systems of care and primary angioplasty techniques, little progress has been made in ameliorating the effects of reperfusion injury, which contributes to final infarct size. Preclinical data indicate that opening of the mitochondrial permeability transition pore plays a major role in reperfusion injury. Cyclosporin is a pharmaceutical inhibitor of cyclophilin D, a major component of permeability transition pore, and therefore there was hope that this agent would improve clinical outcomes, particularly as an earlier phase 2 trial had shown promise. Unfortunately like many other similar trials, cyclosporin did not improve clinical outcomes when compared with placebo. Potential reasons include the formulation used and missing endpoint data with respect to the end-diastolic volume measurements, but the search for a clinically useful agent to reduce reperfusion injury must continue.


Bivalirudin or unfractionated heparin in acute coronary syndromes

Authors: Valgimigli M et al., for the MATRIX Investigators

Summary: This study randomised 7213 patients with acute coronary syndromes for whom PCI was anticipated to receive bivalirudin or unfractionated heparin. Patients in the bivalirudin group were further randomised to receive or not to receive a post-PCI bivalirudin infusion. The rate of major adverse CV events did not differ significantly between the bivalirudin and heparin groups (10.3% and 10.9%, respectively), nor did the rate of net adverse clinical events (11.2% and 12.4%, respectively). Post-PCI bivalirudin infusion did not significantly decrease the rate of urgent TVR, definite stent thrombosis or net adverse clinical events compared with no post-PCI infusion.

Comment: The MATRIX trial was designed to address three differing aspects around comparing bivalirudin with unfractionated heparin and discretionary glycoprotein-IIb/IIIa inhibitor use (25.9% unfractionated heparin group in PCI for acute coronary syndromes. The radial versus femoral access study has been reported previously, but the current trial reports outcomes around the comparisons between agents and whether prolonging the bivalirudin infusion post-PCI was beneficial. There was no clear difference between the agents. It was hypothesised that prolonging the bivalirudin infusion either 4 hours at full dose or 6 hours at reduced dose would allow time for oral P2Y12 agents (46% clopidogrel) to achieve optimal platelet inhibition and therefore reduce the early hazard that has been shown in previous bivalirudin trials. However, there appeared to be no benefit in prolonging the infusion in this study, including with respect to stent thrombosis (1.3% post-PCI, 0.7% no post-PCI). Overall the results continue to inform clinicians around the use of bivalirudin in this clinical context.


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