Interventional Cardiology Research Review™

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Issue 29 - 2020

In this issue:

Abbreviations used in this issue:

ACS = acute coronary syndrome; **ASD** = atrial septal defect; **BAV** = balloon aortic valvuloplasty; **BP** = blood pressure; **DAPT** = dual antiplatelet therapy; **DES** = drug-eluting stent; **IABP** = intra-aortic balloon pump; **LVAD** = left ventricular assist device; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **SAVR/TAVR** = surgical/transcatheter aortic valve replacement; **STEMI** = ST-segment elevation **MI**; **SVC** = superior vena cava.

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Welcome to issue 29 of Interventional Cardiology Research Review.

A trial published in the N Engl J Med comparing clinically relevant bleeding risks in high-risk patients who had undergone PCI and who had received ticagrelor with versus without aspirin begins this issue. This is followed by a paper from the Lancet reporting less target lesion failure at 1 year with a biodegradable polymer sirolimus-eluting stent than with a durable polymer everolimus-eluting stent in patients with acute STEMI undergoing primary PCI. Meanwhile, other included research has reported noninferiority for composite safety and effectiveness outcomes between a polymer-based zotarolimus-eluting stent and a polymer-free drug-coated stent in high-risk patients who received post-PCI DAPT for 1 month. This issue concludes with research evaluating the effect of implanting a covered stent in the SVC (superior vena cava) to redirect SVC flow to the right atrium and right upper pulmonary vein flow to the left atrium in patients with a superior sinus venosus ASD (atrial septal defect).

We hope you find the research selected for this issue interesting and helpful in your everyday practice. We appreciate your comments and feedback, so please keep them coming.

Kind Regards,

Associate Professor Craig Juergens

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Ticagrelor with or without aspirin in high-risk patients after PCI

Authors: Mehran R et al.

Summary: After 3 months of treatment with ticagrelor plus aspirin, 7119 high-risk patients who had undergone PCI and had not had a major bleeding or ischaemic event were randomised to continue ticagrelor with aspirin or placebo for 1 year. The primary endpoint (Bleeding Academic Research Consortium type 2, 3 or 5 bleeding during 1 year) occurred in a lower proportion of ticagrelor plus placebo recipients compared with ticagrelor plus aspirin recipients (4.0% vs. 7.1%; hazard ratio 0.56 [95% CI 0.45–0.68]). The incidence of death from any cause, nonfatal MI or nonfatal stroke was 3.9% in both groups (p<0.001 for noninferiority).

Comment: Historically, patients who undergo DES insertion were recommended 12 months of DAPT, particularly in the context of an ACS. After 12 months, the second antiplatelet therapy is generally stopped and aspirin is continued. This large, multicentre, blinded, randomised, controlled trial examined the effect of stopping aspirin at 3 months and continuing ticagrelor alone versus traditional DAPT on a primary bleeding endpoint. Trial patients had to be at high bleeding or ischaemic risk, and interestingly, 33% of patients did not have an ACS. These were selected patients who had not had a bleeding or ischaemic endpoint in the first 3 months before randomisation. Not surprisingly, there was less bleeding with ticagrelor monotherapy, which did not come at a cost of increased ischaemic endpoints, although it was not powered for this. The results suggest that monotherapy after 3 months with a potent antiplatelet may be reasonable in a cohort of patients after receiving a DES.

Reference: N Engl J Med 2019;381:2032–42
Abstract

Biodegradable polymer sirolimus-eluting stents versus durable polymer everolimus-eluting stents in patients with ST-segment elevation myocardial infarction (BIOSTEMI)

Authors: Iglesias JF et al.

Summary: Adults with acute STEMI referred for primary PCI were randomised to implantation of a biodegradable polymer sirolimus-eluting stent (Orsiro; evaluable n=614) or a durable polymer everolimus-eluting stent (Xience Xpedition/Alpine; evaluable n=626) in the BIOSTEMI trial. Compared with the durable polymer stent, the biodegradable polymer was associated with a lower proportion of participants with target lesion failure (4% vs. 6%; rate ratio 0.59 [95% credibility interval 0.37–0.94]), with no significant between-group difference for cardiac-related death, target-vessel myocardial reinfarction, clinically-indicated target lesion revascularisation or definite stent thrombosis, over 12 months of follow-up.

Comment: Studies have shown superior outcomes in STEMI patients treated with DESs versus bare-metal stents, but to date there have been no large-scale randomised trials comparing newer-generation DESs with each other. This investigator-initiated multicentre trial compared the Orsiro (Biotronik) ultrathin cobalt-chromium (sirolimus-eluting/biodegradable polymer) with the Xience Xpedition (Abbott Vascular) thin-strut cobalt chromium (everolimus-eluting/permanent polymer) stent in an all-comer STEMI cohort. Around 5% of patients were lost to follow-up and there was no routine angiographic follow-up; however, the results suggest superiority of the Orsiro stent for the primary endpoint, mainly driven by a reduced need for ischaemia-driven target-vessel revascularisation. Notably the harder endpoints of cardiac death, MI and stent thrombosis were very similar between the two stents at 1 year. Longer-term follow-up would be interesting to assess the impact of loss of the polymer in the Orsiro arm.

Reference: Lancet 2019;394:1243–53
Abstract

Five-year outcomes of transcatheter or surgical aortic-valve replacement

Authors: Makkar RR et al., for the PARTNER 2 Investigators

Summary: This analysis of the PARTNER 2 randomised study evaluated 5-year outcomes after TAVR versus SAVR in 2032 intermediate-risk patients with severe aortic stenosis, stratified according to intended transfemoral (76.3%) or transthoracic (23.7%) access. During 5 years of follow-up, the incidence of all-cause mortality or disabling stroke did not differ significantly between the TAVR and SAVR groups. Results were similar for the transfemoral-access cohort, but the incidence of death or disabling stroke was higher after TAVR than after SAVR in the transthoracic-access cohort (59.3% vs. 48.3%; hazard ratio 1.32 [95% CI 1.02–1.71]). Repeat hospitalisations were more common after TAVR than after SAVR (33.3% vs. 25.2%), as were aortic valve reinterventions (3.2% vs. 0.8%). At 5 years, more participants from the TAVR group than the SAVR group had at least mild paravalvular aortic regurgitation (33.3% vs. 6.3%).

Comment: There are limited data on long-term clinical outcomes and bioprosthetic valve function after TAVR. This study reported 5-year follow-up of the PARTNER 2 cohort A trial of intermediate surgical risk, severe aortic stenosis patients. Clinical outcomes were comparable between the TAVR (second-generation Sapien XT valve) and surgical patients overall, but worse in the TAVR group when transfemoral access was not used. Valvular function was not quite as good in the TAVR group when compared with surgery. There was a concerning divergence of events in favour of surgery between 2 and 5 years, but we would expect improvements in outcomes in the TAVR group using current generation smaller diameter devices where transthoracic access is used very infrequently and more accurate valve sizing using CT results in less frequent paravalvular regurgitation. The device used is no longer in clinical use and we need yet longer-term follow-up data, but the results are reassuring.

Reference: N Engl J Med 2020;382:799–809
Abstract

Alcohol-mediated renal denervation using the Peregrine System Infusion Catheter for treatment of hypertension

Authors: Mahfoud F et al.

Summary: The use of alcohol-mediated renal denervation using a novel catheter system (Peregrine System™ Infusion Catheter), for infusing dehydrated alcohol as a neurolytic agent into the renal periarterial space, was evaluated in 45 patients with hypertension uncontrolled by ≥3 antihypertensive medications. At 6 months postprocedure, the respective mean 24-hour ambulatory systolic and diastolic BP reductions from baseline were –11 and –7mm Hg (both p<0.001), the respective reductions for office BP measurements were –18 and –10mm Hg, and 23% and 6% of participants had decreases and increases in antihypertensive medications, respectively, with no significant changes in adherence. Nearly all participants (96%) met the primary safety endpoint of absence of periprocedural major vascular complications, major bleeding, acute kidney injury or death at 1 month. There were two cases of periprocedural access-site pseudoaneurysms, one with major bleeding, and there were no deaths, MIs, strokes, transient ischaemic attacks or renal artery stenoses. The respective incidences of left and right main renal arterial transient microleaks were 42% and 49%. Two minor vessel dissections occurred, both of which resolved without treatment.

Comment: The renal sympathetic nerves are involved in the development and maintenance of hypertension, and have been the target of a number of catheter-based renal denervation technologies with variable success. This prospective, single-arm, open-label study reports results using the Peregrine catheter, which delivers microdoses of dehydrated alcohol via curved needles locally into the periadventitial space of the renal artery. Objective measures of treatment adherence using urine analysis were used, and there were significant reductions in ambulatory and office-based BP measurements. The procedure duration was reasonably short at 49 mins (range 22–135) and was reasonably painless when compared to the use of radiofrequency energy. Clearly sham-controlled randomised studies are needed to further assess this novel technology, but these initial results are encouraging.

Reference: JACC Cardiovasc Interv 2020;13:471–84
Abstract

The REDUCE HTN: REINFORCE: randomized, sham-controlled trial of bipolar radiofrequency renal denervation for the treatment of hypertension

Authors: Weber MA et al.

Summary: Patients with pharmacologically untreated hypertension were randomised to active bipolar radiofrequency renal denervation (n=34) or a sham procedure (n=17) in the REDUCE HTN: REINFORCE study; antihypertensive medications could be started after 8 weeks. Enrolment to the trial was terminated early due to apparent futility. The respective mean 24-hour systolic BP reductions in the renal denervation and control groups at 8 weeks did not differ significantly (–5.3 vs. –8.5mm Hg [p=0.30]); however, decreases in systolic BP favouring the denervation group were apparent at 6 months (differences, –7.2, –9.7 and –11.4mm Hg for 24-hour, daytime ambulatory and office measurements, respectively [p values 0.08, 0.02 and <0.01]). Over 12 months of follow-up, one participant from the renal denervation group experienced hypertensive urgency and one experienced progression of renal artery stenosis.

Comment: This study in the same issue of JACC Cardiovasc Interv describes the longer-term results of the Vessix radiofrequency catheter (Boston Scientific) in patients with hypertension not receiving medications at baseline, which had been terminated early for apparent futility. This was a randomised, multicentre, sham-controlled study of a bipolar radiofrequency denervation system. Unlike the original observations, where there was no significant reduction in BP at 8 weeks, follow-up at 6 months showed an advantage in the renal denervation group. Importantly, the reduction was sustained at 12 months. The study is underpowered given the premature termination of enrolment, and there was no measurement of drug adherence using plasma and urine testing, but future trials should factor in longer-term observation.

Reference: JACC Cardiovasc Interv 2020;13:461–70
Abstract

Low-dose alteplase during primary percutaneous coronary intervention according to ischemic time

Authors: McCartney PJ et al., for the T-TIME Investigators

Summary: Patients presenting with STEMI and scheduled for primary PCI at UK hospitals were randomised to receive intracoronary alteplase 10mg (n=144), alteplase 20mg (n=145) or placebo (n=151) in this prospective dose-ranging study; ischaemia durations (time from symptom onset to coronary reperfusion) were <2, 2–<4 and 4–6 hours for 107, 235 and 98 participants, representing prespecified subgroups of interest. No significant association was seen between alteplase dose and the degree of microvascular obstruction (primary outcome; p=0.128 for trend). Moreover, among participants with an ischaemia duration of 4–6 hours, alteplase was associated with greater microvascular obstruction compared with placebo (3.11% and 5.20% for alteplase 10mg and 20mg, respectively, vs. 1.14% [p=0.009 for trend]). A significant interaction was seen between ischaemia duration and alteplase dose (p=0.018).

Comment: Primary PCI has revolutionised the treatment of STEMI, but its success can be compromised by the development of microvascular obstruction. Many agents have been tried and failed to demonstrate superiority to routine PCI to avoid this complication. This placebo-controlled study assessed the utility of adjunctive low-dose intracoronary thrombolysis using alteplase prior to stent implantation in patients with impaired coronary flow at baseline. The primary outcome was the amount of microvascular obstruction as determined by cardiac magnetic resonance. The main conclusion was that the treatment was feasible but not effective. In fact, in a *post hoc* exploratory analysis, there was a suggestion of worse outcomes with ischaemia times of ≥4 hours, which may be related to increased myocardial haemorrhage. The study was terminated early due to prespecified futility criteria and was not powered for clinical endpoints. We await the results of large-scale studies such as the Australian RESTORE-MI study, but we should pay particular attention to patients with a prolonged ischaemia time.

Reference: J Am Coll Cardiol 2020;75:1406–21
Abstract

Interventional Cardiology Research Review™

Independent commentary by Associate Professor Craig Juergens
Associate Professor Craig Juergens is an Interventional Cardiologist at Liverpool Hospital where he is Head of Cardiology. He established the coronary interventional service at Liverpool hospital which has subsequently become a centre of training for interventional Cardiologists. Apart from his interest in Interventional Cardiology, he has a major interest in acute coronary syndromes and has been involved in a large number of multicentre, multinational clinical trials. He has been author of over 90 peer reviewed papers and he continues as an active clinician in the Department of Cardiology at Liverpool Hospital, as well as providing support for the interventional Cardiology programme at Orange Base hospital.

Polymer-based or polymer-free stents in patients at high bleeding risk

Authors: Windecker S et al., for the ONYX ONE Investigators

Summary: Patients at high risk of bleeding who had undergone PCI and then received 1 month of DAPT followed by single antiplatelet therapy were randomised to polymer-based zotarolimus-eluting (n=1003) or polymer-free umirolimus-coated (n=933) stent implantation in this noninferiority trial. There was no significant difference in the 1-year incidence of cardiac-related death, MI or stent thrombosis (composite primary outcome) between the zotarolimus-eluting stent versus the polymer-free drug-coated stent group (17.1% vs. 16.9% [p=0.01 for noninferiority]) or for target-lesion failure (composite of cardiac-related death, target-vessel MI or clinically indicated target-lesion revascularisation; principal secondary outcome; 17.6% vs. 17.4% [p=0.007 for noninferiority]).

Comment: Up to a third of PCI patients are at high bleeding risk and are excluded from many randomised trials due to perceived limitations in tolerability of prolonged DAPT. The LEADERS FREE trial showed that the polymer-free umirolimus-coated BioFreedom stent (Biosensors) was superior to a bare-metal stent in patients at high bleeding risk who received 1 month of DAPT. The current single-blind study compared the polymer-based zotarolimus-eluting Onyx stent (Medtronic) with the BioFreedom stent in a similar design. Stent thrombosis and other ischaemic events were infrequent after 30 days in both groups, even though around 50% of patients presented with an ACS. The results suggest the Onyx stent is noninferior (and may be more deliverable) to the BioFreedom stent and provides more evidence-based treatment options for these difficult patients.

Reference: N Engl J Med 2020;382:1208–18
Abstract

Prior balloon valvuloplasty versus direct transcatheter aortic valve replacement

Authors: Leclercq F et al.

Summary: In the open-label, randomised, noninferiority DIRECTAVI trial, 236 patients underwent TAVR using the Edwards SAPIEN 3 valve with or without prior BAV (balloon aortic valvuloplasty); seven participants from the direct implantation group required BAV to cross the valve. The overall device success rate was 78.0%, with the noninferiority criterion met between the BAV versus non-BAV group (75.5% vs. 80.2% [p=0.02 for noninferiority]). There were no cases of severe prosthesis-patient mismatch or severe aortic regurgitation. There was no significant difference between the BAV and direct implantation groups for adverse events related to pacemaker implantation (20.9% vs. 19.0% [p=0.70]), procedure duration, contrast volume, radiation exposure or postdilatation rate.

Comment: BAV is generally considered a mandatory step before TAVR; however, it can be associated with a number of potential complications. Therefore, avoiding BAV may reduce complications, especially with new generations of lower profile TAVR. The current prospective, single-centre, randomised, open-label study showed that direct TAVR without prior BAV was noninferior to the conventional technique when using the SAPIEN 3 balloon expandable valve. Notably, procedure times, contrast volumes, radiation doses and need for postdilatation were not statistically different between groups. Also notably, in 5.8% of patients with challenging anatomy, direct TAVR was not possible. The study doesn't establish whether we can do away with routine predilatation in all patients as more than a third of screened subjects were excluded, but it would be reasonable in a select group without challenging anatomy to use direct TAVR.

Reference: JACC Cardiovasc Interv 2020;13:594–602
Abstract

Association of use of an intravascular microaxial left ventricular assist device vs intra-aortic balloon pump with in-hospital mortality and major bleeding among patients with acute myocardial infarction complicated by cardiogenic shock

Authors: Dhruva SS et al.

Summary: Outcomes were reported for a retrospective cohort of 28,304 patients (67% male) who underwent PCI for acute MI complicated by cardiogenic shock, treated with mechanical circulatory support devices; 81.3% had STEMI and 43.3% had cardiac arrest. Patients who had received intravascular microaxial LVAD (6.2% of the cohort) were propensity matched with those who had received IABP (29.9%), resulting in 1680 pairs for comparative analyses. Compared with the IABP group, significantly greater proportions of the intravascular microaxial LVAD group died or experienced major bleeding while in hospital (45.0% vs. 34.1% and 31.3% vs. 16.0%, respectively [both p<0.001]); these differences persisted regardless of whether the patients received their device before or after PCI initiation.

Comment: Cardiogenic shock due to acute MI results in high mortality and has led to attempts to use mechanical circulatory support such as an IABP, but randomised trials have failed to show improved mortality using this technology. More recently, enthusiasm for the use of intravascular microaxial LVAD such as the Impella has developed. The current retrospective cohort study using two large USA registries tried to match patients in cardiogenic shock who received either an IABP or a microaxial LVAD to compare outcomes. Somewhat surprisingly, patients did better with an IABP regardless of whether the device was placed before or after PCI. Furthermore, an IABP was no better than medical therapy alone in matched groups. Limitations of the study include: site reporting of shock, use of single timepoint measurements of haemodynamics, lactate level, etc., and possible residual confounding that patients receiving microaxial LVAD were sicker. Further research is needed before this technology is more widely adopted.

Reference: JAMA 2020;323:734–45
Abstract

Transcatheter correction of superior sinus venosus atrial septal defects as an alternative to surgical treatment

Authors: Hansen JH et al.

Summary: These researchers evaluated the implantation of a 10-zig covered Cheatham platinum stent between 5cm and 8cm in length in the SVC to redirect flow from the SVC and right upper pulmonary vein to the right and left atria, respectively, in 48 consecutive patients with a superior sinus venosus ASD. At the time of reporting, 25 patients had undergone the procedure, with six pending and eight deemed technically unsuitable. Nine of the patients also had a second, uncovered stent inserted for anchoring, and four required a high-pressure balloon to protect the right upper pulmonary vein from pulmonary venous obstruction during stent implantation. Unobstructed pulmonary venous return was seen on cardiac CT at 3 months postprocedure. There were no deaths recorded over median follow-up of 1.4 years, one patient developed stent embolisation, and another required haemopericardium drainage. At most recent follow-up, one patient had a residual shunt.

Comment: The superior sinus venosus ASD is situated immediately inferior to the junction of the SVC and the right atrium, and is usually associated with partial anomalous pulmonary venous drainage. Surgical correction is the standard of care, but inspired by a 2013 case series, the current study from London describes a single-centre experience using a transcatheter technique. A covered stent (10-zig covered Cheatham platinum) is placed from the SVC into the right atrium, which simultaneously closes the ASD and redirects pulmonary venous drainage to the left atrium behind the covered stent. Using cross-sectional imaging and *ex vivo* simulation with 3D-printed or virtual models, 40 of 48 patients were considered suitable for the approach (ultimately only 25 had been implanted at the time of reporting). Medium-term results are promising, but longer-term studies are needed before this becomes the new standard of care for these complex patients.

Reference: J Am Coll Cardiol 2020;75:1266–78
Abstract

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