Interventional Cardiology Research Review™

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In this issue:

Abbreviations used in this issue:

ACS/CCS = acute/chronic coronary syndrome; **AF** = atrial fibrillation; **CABG** = coronary artery bypass graft; **CAD** = coronary artery disease; **CV** = cardiovascular; **DAPT** = dual antiplatelet therapy; **DES** = drug-eluting stent; **EF/LVEF** = (left ventricular) ejection fraction; **FFR** = fractional flow reserve; **HR** = hazard ratio; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **RCT** = randomised controlled trial; **STEMI** = ST-segment elevation **MI**; **TAVI** = transcatheter aortic valve implantation; **TEER** = transcatheter edge-to-edge repair; **TMVR** = transcatheter mitral valve replacement; **VKA** = vitamin K antagonist.

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Welcome to issue 35 of Interventional Cardiology Research Review.

We begin this issue with an investigator-initiated, prospective, randomised, open-label, multicentre trial comparing aspirin and clopidogrel monotherapy in patients undergoing coronary stenting. Another RCT found that edoxaban and VKAs were noninferior for adverse clinical events in patients with AF after successful TAVI. A nonrandomised study has evaluated the 2-year safety and effectiveness of TMVR in high-surgical-risk patients with severe mitral regurgitation. The issue concludes with research reporting no evidence that FFR guidance reduces the risk of ischaemic CV events or death at 1-year follow-up in patients with multivessel CAD.

We hope you find the research selected for this review interesting. We appreciate all comments and feedback, and look forward to receiving any you wish to send us.

Kind Regards,

Conjoint Professor Craig Juergens
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Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM)

Authors: Koo B-K et al, on behalf of the HOST-EXAM investigators

Summary: The HOST-EXAM trial compared the use of long-term monotherapy with aspirin versus clopidogrel after PCI. At 37 sites in South Korea, 5438 patients who received DAPT without clinical events for 6–18 months after PCI with a DES were randomised to receive monotherapy with either clopidogrel 75mg once daily or aspirin 100mg once daily for a further 24 months. The primary endpoint was a composite of all-cause death, non-fatal MI, stroke, readmission for ACS and major bleeding. During follow-up, the primary outcome occurred in 5.7% of the clopidogrel group compared with 7.7% of the aspirin group (HR 0.73 [95% CI 0.59–0.90]).

Comment: Standard therapy after PCI is DAPT for 6–12 months with indefinite use of a single agent. This has traditionally been aspirin, but no large randomised trial to date has specifically randomised which antiplatelet in the chronic maintenance phase after DES implantation. This investigator-initiated, prospective, randomised, multicentre open-label trial from South Korea provides such data. The authors found clopidogrel was superior to aspirin in a group of patients who had been stable 6–18 months after their DES. This was true for both thrombotic and bleeding endpoints, although this did not translate into reduced overall death, as there were numerically higher rates of cancer-related deaths in the clopidogrel group, which is not easily explained. Given clopidogrel is generic and cheaper, it would appear we should change the way we think about chronic therapy, although we will need to manage our surgical colleagues who preferentially prefer to operate on patients on aspirin rather than clopidogrel.

Reference: Lancet 2021;397:2487–96
Abstract

Independent commentary by Conjoint Professor Craig Juergens

Professor Craig Juergens is an Interventional Cardiologist at Liverpool Hospital where he is Director of Medicine. 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 100 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.

Safety of selective intracoronary hypothermia during primary percutaneous coronary intervention in patients with anterior STEMI

Authors: El Farissi M et al.

Summary: These researchers reported on the safety of selective intracoronary hypothermia for reducing myocardial reperfusion injury in the first 50 participants enrolled in the ongoing randomised EURO-ICE trial, which is comparing the procedure with standard primary PCI in patients with anterior STEMI. There were no in-hospital deaths reported, one participant from each trial arm developed cardiogenic shock, AF was reported in three participants from the control group but none from the investigational group, ventricular fibrillation occurred in five participants from the investigational group and three from the control group, and two participants from the intracoronary hypothermia group experienced stent thrombosis (one intraprocedural and the other following interruption of DAPT consequent to an intracranial haemorrhage), compared with none in the control group; none of the between-group differences for these complications were statistically significant.

Comment: Whilst experimental studies have shown how hypothermia prior to reperfusion by primary PCI in STEMI reduces infarct size, RCTs of systemic hypothermia have failed to demonstrate a benefit. The current preliminary examination of anterior MI patients with an occluded artery investigates a novel method of providing highly selective intracoronary cooling that produces a lower temperature with less volume of fluid than can systemic cooling. Cooling is achieved in two phases via the lumen of an over the wire balloon, which is inflated at the occlusion site to 4 atm. Initially, saline is infused at room temperature with the balloon inflated and then colder saline (3–4°) is infused as the balloon is deflated. This added only 6 minutes to the procedure. These preliminary results suggest it is safe compared with controls, and we await the final results of the 200-patient study that will look at final infarct size at 3 months as determined by MRI.

Reference: JACC Cardiovasc Interv 2021;14:2047–55
Abstract

Edoxaban versus vitamin K antagonist for atrial fibrillation after TAVR

Authors: Van Mieghem NM et al., for the ENVISAGE-TAVI AF Investigators

Summary: Patients who had undergone TAVI and required oral anticoagulation due to AF were randomised to receive edoxaban (n=713) or a VKA (n=713) in this open-label trial; almost all the participants had a history of AF prior to TAVI. Noninferiority was confirmed for the composite primary efficacy outcome (death from any cause, MI, ischaemic stroke, systemic thromboembolism, valve thrombosis or major bleeding) for edoxaban versus VKAs (17.3 vs. 16.5 per 100 person-years; HR 1.05 [95% CI 0.85–1.31]; p=0.01 for noninferiority), and the all-cause mortality/stroke rate did not differ significantly (10.0 vs. 11.7 per 100 person-years; 0.85 [0.66–1.11]), but there were more major bleeds (mainly gastrointestinal) with edoxaban (9.7 vs. 7.0 per 100 person-years; 1.40 [95% CI 1.03–1.91]).

Comment: AF occurs in about a third of patients undergoing TAVI. There have been no large randomised trials comparing VKAs with new oral anticoagulants in this situation. The current randomised multicentre, open-label study examined the use of edoxaban, an oral reversible direct factor Xa inhibitor, compared with warfarin. The majority of patients (99%) had AF prior to TAVI and edoxaban was proven to be noninferior to warfarin with respect to the primary endpoint. There was a numerically lower rate of death, intracranial haemorrhage and ischaemic stroke, but a higher incidence of predominantly gastrointestinal bleeding in the edoxaban group. Notably, the mean time to randomisation was 66.6–70.2 hours after the TAVI procedure, and bleeding was magnified when there was concomitant antiplatelet use with edoxaban. Based on this study, there would be no imperative to switch from warfarin to edoxaban in patients already on it, particularly if there was a need for concomitant antiplatelet agents.

Reference: N Engl J Med 2021;385:2150–60
Abstract

Dual antiplatelet therapy after PCI in patients at high bleeding risk

Authors: Valgimigli M et al., for the MASTER DAPT Investigators

Summary: The MASTER DAPT trial investigated the efficacy of DAPT in patients at high risk for bleeding after the implantation of a drug-eluting coronary stent. Patients considered to be at high risk for bleeding (n=4434) received 1 month of DAPT after PCI before being randomised to single antiplatelet therapy or continued DAPT for ≥2 more months; a single third-generation sirolimus-eluting stent was used. PCI for ACS was performed in 48.3% of participants, and 36.4% were receiving concomitant anticoagulants. One month of DAPT was noninferior to 3 months of DAPT, both for net adverse clinical events (7.5% vs. 7.7% [p<0.001 for noninferiority]) and major cardiac and cerebral events (6.1% vs. 5.9% [p<0.001 for noninferiority]), and resulted in a lower incidence of major or clinically relevant nonmajor bleeding (6.5% vs. 9.4% [p<0.001]).

Comment: Studies have demonstrated the superiority of DESs over bare-metal stents in patients at high bleeding risk receiving 1 month of DAPT, but the optimal duration of DAPT has not been well studied in this group. The current investigator-initiated, multicentre, multinational, randomised, open-label, noninferiority trial showed 1 month of DAPT was noninferior to 3–6 months in patients receiving the biodegradable polymer sirolimus-eluting Ultimaster (Terumo) DES. Notably, patients had been stable for a median of 34 days after the index procedure before being randomised, and only 48% had undergone PCI for an ACS. Most of the benefit in the abbreviated therapy group was seen in clinically relevant nonmajor bleeding (BARC 2), and there was a numerically higher rate of stent thrombosis in this group. Whilst the data are informative, we should continue to balance the bleeding and ischaemic risk in these complex patients when deciding the appropriate duration of DAPT.

Reference: N Engl J Med 2021;385:1643–55
Abstract

Rivaroxaban monotherapy in patients with atrial fibrillation after coronary stenting

Authors: Matoba T et al., on behalf of the AFIRE Investigators

Summary: These researchers used data from the AFIRE trial of rivaroxaban with versus without antiplatelet therapy in 2215 patients with AF and stable CAD to investigate the benefits of rivaroxaban monotherapy according to time between stenting and enrolment. Compared with combination rivaroxaban/antiplatelet therapy, rivaroxaban monotherapy was superior for the composite efficacy endpoint (stroke, systemic embolism, MI, unstable angina requiring revascularisation and death from any cause; HR 0.70 [95% CI 0.50–0.98]) and the safety endpoint (major bleeding; 0.55 [0.33–0.92]), but not the ischaemic endpoint [0.82 [0.58–1.15]). The HRs decreased as time between stenting and enrolment increased (respective p value for interaction, 0.158 and 0.097 for the efficacy and safety endpoints, respectively).

Comment: The AFIRE study was a multicentre, randomised, open-label trial conducted in Japan in patients with AF and stable CAD. A total of 2236 patients were randomised to either rivaroxaban 10–15mg (depending on renal function) alone or in combination with an antiplatelet agent according to physician preference. The current study looked at the 1444 patients who had undergone stenting more than 12 months from enrolment. Most stents were second-generation DESs (54.2%) followed by bare-metal stents (25.8%). Similar to the overall results, monotherapy was superior to dual therapy for the combined efficacy endpoint. This was true regardless of the time from previous stent placement, although there were fewer patients enrolled between 1 and 2 years after their procedure. There were no stent thromboses in either group. The doses of rivaroxaban were lower than we use, and we do not have data on specific high ischaemic risk patients, but the data support the safe withdrawal of an antiplatelet beyond 1 year in this stable patient cohort.

Reference: JACC Cardiovasc Interv 2021;14:2330–40
Abstract

2-year outcomes of transcatheter mitral valve replacement in patients with severe symptomatic mitral regurgitation

Authors: Muller DWM et al.

Summary: Two-year follow-up data were reported for 100 high-surgical-risk patients with severe (grade 3+ or 4+) mitral regurgitation who underwent transapical TMVR in the open-label Expanded Clinical Study of the Tendyne Mitral Valve System study. Prostheses implantation was successful in 97.0% of these patients. The 2-year all-cause mortality rate was 39.0%, with 43.6% of deaths occurring during the first 90 days. Hospitalisations for HF fell significantly from 1.30 (preprocedure) to 0.51 per year 2 years after TMVR (p<0.0001). After 2 years, there was no mitral regurgitation detected in 93.2% of survivors, and no participant had grade >1+ mitral regurgitation. Symptom improvement at 1 year was sustained out to 2 years with 88.5% and 81.6% of participants in New York Heart Association functional class I or II at these respective timepoints. Among survivors, baseline LVEF had fallen significantly after 2 years (from 45.6% to 39.8% [p=0.0012]), and estimated right ventricular systolic pressure had fallen from 47.6 to 32.5mm Hg (p<0.005).

Comment: TEER (transcatheter edge-to-edge repair) is a viable treatment for suitable patients with severe mitral regurgitation at high surgical risk; however, it is not suitable for all anatomies and persisting mitral regurgitation remains in a significant minority. Therefore, TMVR technologies have been developed, including the Tendyne mitral valve system (Abbott Vascular). This paper presents 2-year results of the first 100 patients enrolled in a prospective, multicentre (including Australian sites) nonrandomised study. The valve was successfully implanted transapically in all but three patients with no procedural deaths. Five patients required reintervention and valve thrombosis occurred within 6 months in six. Major, including fatal, bleeding occurred in 27 patients at 2 years. The near elimination of mitral regurgitation and improvement in symptoms in survivors was sustained, but the 2-year mortality was quite high (39%) despite stringent selection criteria. Twelve patients were lost to follow-up and <50% had echocardiography at 2 years, which is not ideal. We have a lot to learn before TMVR can compete with TEER and surgical repair/replacement.

Reference: J Am Coll Cardiol 2021;78:1847–59
Abstract

3-year clinical outcomes after implantation of permanent-polymer versus polymer-free stent

Authors: van Hemert ND et al., ReCre8 Study Investigators

Summary: Long-term clinical outcomes (1- to 3-year follow-up) were reported in this landmark analysis of the ReCre8 trial, in which 1491 all-comers undergoing PCI with DES implantation were randomised to implantation of the polymer-free Amphilimus™ (sirolimus plus fatty acid)-eluting coronary stent or a permanent polymer zotarolimus-eluting stent. Noninferiority was evident for the polymer-free stent versus the permanent polymer for the endpoint of target lesion failure (5.1% vs. 4.9% [p=0.0031 for noninferiority]).

Comment: The Cre8 (Alvmedica) is a thin-strut, polymer-free Amphilimus-eluting stent covered with an ultrathin carbon coating. In the ReCre8 randomised controlled, investigator-initiated trial comparing this and the permanent polymer Resolute integrity stent (Medtronic Vascular), the Cre8 stent was found to be noninferior at 1 year with respect to target lesion failure. The current study presents 3-year data and confirms no significant difference in outcomes between the two stent platforms. This was true also in the subset of patients with diabetes mellitus where preliminary data had suggested a potential advantage of the Cre8 stent. There was only one late-stent thrombosis in the Resolute group and none in the Cre8 group. Notably non-ACS patients only received 1 month of DAPT. The current results suggest no unique advantage of a polymer-free stent, but confirm robust long-term results for this new iteration of DESs.

Reference: JACC Cardiovasc Interv 2021;14:2477–86
Abstract

Pretreatment with P2Y12 inhibitors in patients with chronic coronary syndrome undergoing percutaneous coronary intervention

Authors: Jurga J et al.

Summary: Pretreatment with P2Y12 inhibitors (n=18,577) was compared with treatment in the catheterisation laboratory (n=8237) in a real-world population of Swedish registrants with CCSs undergoing *ad hoc* PCI. Compared with pretreatment, patients treated in the catheterisation laboratory had lower risks of net adverse clinical events (death, MI, stroke and bleeding; 4.2% vs. 5.1%, adjusted HR 0.79 [CI 0.63–0.99]), bleeding (2.3% vs. 2.6%, 0.76 [0.57–1.01]) and in-hospital bleeding (1.9% vs. 2.1%, adjusted odds ratio 0.70 [0.51–0.96]), and there was no significant difference for the risk for death, MI or stroke. Among patients treated in the catheterisation laboratory, those treated with ticagrelor or prasugrel (received by 41%) versus clopidogrel (59%) had higher risks of net adverse clinical events (5.4% vs. 3.4%, adjusted HR 1.66 [CI 1.12–2.48]), bleeding (3.4% vs. 1.6%; 2.14 [1.34–3.42]) and in-hospital bleeding (2.9% vs. 1.2%; adjusted odds ratio 2.24 [1.29–3.90]), but similar risks of death, MI and stroke.

Comment: DAPT is the mainstay of treatment after PCI, and whilst aspirin is routinely prescribed pre-intervention, there is some controversy around the timing of administration of the second antiplatelet (P2Y12 inhibitor) in relation to the intervention in patients with CCSs. This is a retrospective analysis of prospectively collected data from the all-comer Swedish Coronary Angiography and Angioplasty Registry of patients with a CCS undergoing *ad hoc* PCI. Radial access was used in 69% of cases and clopidogrel was the P2Y12 used in 90% of pretreated and 59% of in-lab treated patients. Whilst not randomised, this large study does not support routine pretreatment of such patients scheduled for angiography with or without PCI, as it results in more bleeding without a reduction in ischaemic endpoints. The increase in bleeding was magnified in patients pretreated with prasugrel or ticagrelor, which technically are not indicated in CCSs. Avoiding pretreatment before coronary anatomy is known also has the advantage of expediting CABG if required.

Reference: Circ Cardiovasc Interv 2021;14:e010849
Abstract

Early hospital discharge following PCI for patients with STEMI

Authors: Rathod KS et al.

Summary: A novel early hospital discharge pathway for low-risk STEMI patients was assessed in this research, which included 600 patients deemed to be at low risk for early major adverse CV events and successfully discharged in <48 hours. Structured telephone follow-up interviews at 48 hours postdischarge and virtual follow-up assessments at 2, 6 and 8 weeks and 3 months were undertaken. The median length of hospital stay was 24.6 hours, compared with 65.9 hours before the pathway was instigated. There were two deaths over a median 271 days of follow-up, both due to COVID-19. There were no deaths due to CV causes and the major adverse CV event rate was 1.2%, with these findings comparing favourably in unadjusted and propensity-matched analyses of historical control data from 700 patients who met the same pathway criteria and remained in hospital for >48 hours, for whom the respective mortality and major adverse CV event rates were 0.7% and 1.9%.

Comment: Early hospital discharge after primary PCI for STEMI has become increasingly accepted, with a number of RCTs having shown that discharge of low-risk individuals at day 2–3 was safe. The current observational study from a single high-volume centre in England showed discharge within 48 hours (median 24.6 hours) of low-risk patients was safe in conjunction with very close telemedicine follow-up when compared with a similar group of patients kept at physician discretion. Low-risk status included EF ≥40%, successful PCI (TIMI 3 flow), absence of planned staged inpatient revascularisation, no recurrent ischaemia, heart failure or arrhythmias and appropriate social support. Radial access was used in 94% of cases, and patients were treated early after symptom onset (median 80 minutes). Whilst not a randomised trial, we could consider using these criteria to free up much-needed beds and reduce risks of in-hospital transmission of the coronavirus. This would be contingent on the ability to provide early in-person or telemedicine follow-up to allow important rehabilitation and education to be provided.

Reference: J Am Coll Cardiol 2021;78:2550–60
Abstract

Fractional flow reserve to guide treatment of patients with multivessel coronary artery disease

Authors: Rioufol G et al., on behalf of the FUTURE Trial Investigators

Summary: The FUTURE trial randomised patients with candidate multivessel CAD to a treatment strategy based on FFR in all stenotic (≥50%) coronary arteries (revascularisation indicated for FFR ≤0.80 lesions) or a traditional strategy without FFR; the trial was terminated prematurely after a safety analysis, at which time 927 patients had been enrolled. After 1 year of follow-up, no significant difference was evident between the FFR versus non-FFR groups for the major adverse cardiac or cerebrovascular event rate (primary endpoint; 14.6% vs. 14.4% [p=0.85]) and a higher all-cause mortality rate did not reach statistical significance (3.7% vs. 1.5% [p=0.06]); these findings were confirmed at 24 months' extended follow-up. FFR was associated with a significantly lower proportion of participants who underwent revascularisation with more referred for exclusive medical treatment (p=0.02).

Comment: Most trials of FFR have restricted recruitment to patients who were suitable for PCI. The current multicentre, open-label RCT allowed patients with multivessel disease in whom PCI, CABG or medical therapy could be considered, and randomised them to either FFR or angiographic-guided treatment. The trial was terminated early by the data safety and monitoring board after interim analysis showed increased mortality in the FFR-guided arm, although this difference was no longer significant after all the data were collected and analysed. Possible reasons for the unexpected findings include: investigators at their discretion stented >20% of FFR-negative lesions, resulting in similar stent usage in both groups; more patients received medical therapy alone (17% vs. 9%) in the FFR-guided arm; and patients not suitable for PCI or with left main disease were included, unlike other FFR-guidance trials. Whilst the results are somewhat discordant with other FFR trials, it may be that angiographic guidance is best in sicker patients with more complex disease (especially EF <40% and a SYNTAX score >32).

Reference: J Am Coll Cardiol 2021;78:1875–85
Abstract

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