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; **CTO** = chronic total occlusion; **CV** = cardiovascular; **DOAC** = direct oral anticoagulant; **FFR** = fractional flow reserve; **HR** = hazard ratio; **LAAC** = left atrial appendage closure; **MI** = myocardial infarction; **PCI** = percutaneous coronary intervention; **QFR** = quantitative flow ratio; **QOL** = quality of life.

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Welcome to issue 36 of Interventional Cardiology Research Review.

This issue begins with research reporting 10-year all-cause mortality in the SYNTAXES trial of CABG versus PCI according to the diabetes status of the participants. We have also included the 4-year outcomes from the PRAGUE-17 trial, which has previously reported noninferiority between LAAC (left atrial appendage closure) and DOACs for preventing major neurological, CV or bleeding events in high-risk patients with AF. The penultimate paper in this issue is an economic evaluation of PCI across a range of indications undertaken by colleagues from Monash University in Victoria, and the issue concludes with research reporting cardiac-related death rates according to MI definition used for patients with CCS (chronic coronary syndromes) undergoing PCI.

We hope you find this update in interventional cardiology research enlightening, and we look forward to receiving your comments and feedback.

Kind Regards,

Professor Craig Juergens
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Ten-year all-cause death after percutaneous or surgical revascularization in diabetic patients with complex coronary artery disease

Authors: Wang R et al.

Summary: Ten-year mortality rates were reported for 1800 participants with three-vessel disease and/or left main CAD from the randomised SYNTAXES study of CABG versus PCI, according to diabetes mellitus status. Among participants with diabetes (n=452), those who underwent PCI had a numerically higher 5-year mortality rate than those who underwent CABG (19.6% vs. 13.3%; HR 1.53 [95% CI 0.96–2.43]), but the risk was lower during years 5–10 (20.8% vs. 24.4%; 0.82 [0.52–1.27]). There was no significant difference in 10-year mortality between the PCI versus CABG group for diabetics (36.4% vs. 34.5% [p=0.551]) or for nondiabetics, but a numerical increase in risk was noted for the subgroup of 182 insulin recipients (47.9% vs. 39.6% [p=0.227]).

Comment: Based on trials such as FREEDOM, guidelines recommend CABG over PCI in patients with diabetes mellitus, particularly those with multivessel coronary disease. The current study reports long-term follow-up of patients originally enrolled in the SYNTAXES trial, which was an all-comer trial of patients with *de novo* three-vessel disease and/or left main coronary disease who were suitable for either CABG or first-generation drug-eluting stent PCI. With respect to the 452 diabetic patients, mortality was increased in the overall cohort (35.4% vs. 23.6%; p<0.001) when compared with the nondiabetic cohort. Mortality was numerically higher in the PCI group at 5 years, but the opposite was seen between 5 and 10 years, meaning there was only a marginally higher mortality rate in the PCI group at 10 years (36.4% vs. 34.5%). There was no significant difference between PCI or CABG in diabetic patients regardless of anatomical SYNTAX score tertile. There was numerically higher mortality in the 182 insulin-requiring diabetic patients (47.9% vs. 39.6%). The results suggest whilst the presence of diabetes is an adverse risk factor for longevity, the choice of revascularisation strategy in patients with multivessel disease should be individualised.

Reference: Eur Heart J 2022;43:56–67
Abstract

Independent commentary by 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.

Angiography after out-of-hospital cardiac arrest without ST-segment elevation

Authors: Desch S et al., for the TOMAHAWK Investigators

Summary: The TOMAHAWK trial evaluated the benefits of early coronary angiography and revascularisation in 554 patients with successfully resuscitated out-of-hospital cardiac arrest of possible coronary origin. Patients were randomised to undergo either immediate coronary angiography (immediate-angiography group) or initial intensive care assessment with delayed or selective angiography (delayed-angiography group). None of the patients had evidence of ST-segment elevation on post-resuscitation ECG. By 30 days, 54.0% of patients in the immediate-angiography group and 46.0% in the delayed-angiography group had died (HR 1.28 [95% CI 1.00–1.63]). The composite of death or severe neurological deficit occurred more frequently in the immediate-angiography group (64.3% vs. 55.6%).

Comment: People suffering out-of-hospital cardiac arrest have extremely high mortality even if initially resuscitated. Whilst there is general agreement that patients with ST-segment elevation should go emergently to the cath lab, there are few data supporting such an approach in the absence of ST-segment elevation. This study was an international, investigator-initiated, multicentre, randomised, open-label trial, and included patients with both shockable and nonshockable arrest rhythms. The majority of patients received targeted temperature management, although this was delayed by around 34 minutes in the immediate-angiography group. One or more potential culprit lesions for the arrest were identified in 38.1% and 43% of patients undergoing immediate and delayed angiography, respectively. The results suggest that performing early unselected angiography (median 2.9 hours after arrest) and undergoing revascularisation where appropriate was not superior to a delayed or selective strategy of angiography (median 46.9 hours after arrest). These results are consistent with the COACT (which only included a shockable arrest rhythm) and two smaller similar randomised trials, and suggest we should be highly selective in taking such patients to the cath lab in the absence of ST-segment elevation.

Reference: N Engl J Med 2021;385:2544–53
Abstract

Fractional flow reserve-guided PCI as compared with coronary bypass surgery

Authors: Fearon WF et al., for the FAME 3 Investigators

Summary: This noninferiority trial randomised 1500 patients with three-vessel CAD to undergo CABG or FFR (fractional flow reserve)-guided PCI with current-generation zotarolimus-eluting stents. The 1-year incidence of the composite primary endpoint (death from any cause, MI, stroke or repeat revascularisation) was 10.6% with FFR-guided PCI and 6.9% with CABG (HR 1.5 [95% CI 1.1–2.2]; p=0.35 for noninferiority), and the respective 1-year incidences of the composite of death, MI and stroke were 7.3% and 5.2% (1.4 [0.9–2.1]). CABG was associated with higher incidences of major bleeding, arrhythmias and acute kidney injury than FFR-guided PCI.

Comment: Whether PCI or CABG is a superior revascularisation strategy in patients with multivessel disease has been the subject of debate and randomised controlled trials for decades. The current multicentre, international (including Australian sites), noninferiority trial is the first to evaluate such patients when PCI was guided by FFR. FFR-guided PCI was not noninferior to CABG with respect to the primary endpoint. There are some limitations, including that the PCI procedures were infrequently guided by intravascular imaging (11.7%), which could have potentially improved outcomes. Multiple arterial grafts were only used in 24.5%, so this may in fact have underestimated the benefits of CABG. Follow-up was only to 1 year, and we would expect the benefits of CABG to further accrue overtime. The majority of patients presented with stable coronary syndromes (61%), and in light of the ISCHEMIA trial, a control arm would have been interesting in this subset. The FAME-3 trial adds to the burden of data suggesting CABG is a superior revascularisation strategy than PCI for patients with multivessel disease when surgical risk is not prohibitive.

Reference: N Engl J Med 2022;386:128–37
Abstract

Distal or traditional transradial access site for coronary procedures

Authors: Tsigkas G et al.

Summary: Consecutive patients scheduled for coronary procedures at a single centre were randomised to a right distal transradial approach (n=518) or the conventional transradial approach (n=524) in this trial; 78.0% and 74.8% of the respective study arms successfully underwent follow-up Doppler radial artery evaluation. Compared with the conventional transradial approach, the distal transradial approach was associated with a lower radial artery occlusion rate (primary endpoint; 3.7% vs. 7.9% [p=0.014]), a lower rate of successful sheath insertion (78.7% vs. 94.8% [p<0.001]), a greater median number of punctures (2 vs. 1 [p<0.001]), a longer time required for sheath insertion (120 vs. 75 sec [p<0.001]), a shorter haemostasis time (60 vs. 120 minutes [p<0.001]) and a higher median dose area product (32,729 vs. 28,909 cGy/cm^2 [p=0.02]). There was no significant between-group difference for bleeding or for severe radial artery spasm.

Comment: Radial artery access has become the default approach in performing coronary interventional procedures to minimise bleeding complications, but radial artery occlusions have been reported in 1–33% of patients. New techniques to minimise radial artery occlusion include the use of distal radial access, as this potentially maintains anterograde flow in the forearm during haemostasis via the palmar arch. The current single-centre study from Greece is the largest to date evaluating this technique, and confirmed quicker haemostasis and a much lower rate of radial artery occlusion in the distal radial group, although the rate in the conventional arm (7.9%) was higher than in other studies. This came at the cost of longer access and procedural times, and the frequent need to crossover to alternative access (21.8%). Notably there was a low rate of PCI performed (24.6%) and a predominance of 5Fr sheaths used, and how the technique would compare in more complex procedures and larger sheaths remains to be determined. However, results could improve with operator experience, routine ultrasound guidance and differing access needles. Clearly more studies are needed, but the current study sets a good platform for future research.

Reference: JACC Cardiovasc Interv 2022;15:22–32
Abstract

Acetylcholine rechallenge: a first step toward tailored treatment in patients with coronary artery spasm

Authors: Seitz A et al.

Summary: Patients with coronary spasms (55 with microvascular spasm and 40 with epicardial spasm) during initial acetylcholine provocation underwent repeated acetylcholine provocation 3 minutes after intracoronary glyceryl trinitrate (nitroglycerin) administration at the same dose that induced the initial spasm. Among the patients with initial epicardial spasm, acetylcholine rechallenge revealed that 48% had coexisting glyceryl trinitrate-persistent microvascular spasm. Re-induction of epicardial spasm was prevented by glyceryl trinitrate administration prior to acetylcholine rechallenge in 100% and 80% of patients with focal and diffuse spasms, respectively. Prior glyceryl trinitrate administration prevented microvascular spasm in only 20% of patients, but was able to attenuate it in a further 49%.

Comment: Coronary artery spasm is a frequent mechanism of angina in patients with nonobstructive coronary disease. Acetylcholine is now the preferred agent to provoke epicardial coronary artery spasm. There is another form of abnormal acetylcholine response called microvascular spasm, where chest pain and ECG changes occur in the absence of epicardial vasospasm, although both can exist concurrently (discovered in up to 50% of patients in this study). This novel multicentre registry study evaluated the feasibility and safety of acetylcholine rechallenge in the one sitting, and potentially proposes a pathway for assessing these complex patients. Patients were on average 61 years old and 69% were female. They found that glyceryl trinitrate successfully prevented diffuse epicardial spasm in 80% of patients, but only 20% of those with microvascular spasm, although it attenuated the effect in a further 49%. It remains to be seen if responses in the cath lab translate into benefits in the real world, and ideally a placebo should have been used to remove bias, but the study should act as an exemplar for more research in this area, potentially in conjunction with a standardised approach to dosages used.

Reference: JACC Cardiovasc Interv 2022;15:65–75
Abstract

4-year outcomes after left atrial appendage closure versus nonwarfarin oral anticoagulation for atrial fibrillation

Authors: Osmancik P et al., on behalf of the PRAGUE-17 Trial Investigators

Summary: The PRAGUE-17 trial demonstrated that LAAC was noninferior to DOACs for preventing major neurological, CV and bleeding events in high-risk patients with AF. This report described prespecified long-term outcomes in 402 PRAGUE-17 participants (mean age 73.3 years, 65.7% male). During a median 3.5 years of follow-up, LAAC was noninferior to DOACs for the primary composite endpoint of cardioembolic events, CV-related death, clinically-relevant bleeding or procedure/device-related complications (p=0.006 for noninferiority). LAAC decreased nonprocedural clinically-relevant bleeding compared with DOACs (subdistribution HR 0.55 [95% CI 0.31–0.97]), but none of the other individual components of the composite endpoint differed significantly between groups.

Comment: The PRAGUE-17 trial was a multicentre, investigator-initiated, open label, randomised, noninferiority trial comparing percutaneous LAAC with DOACs. The initial results at 20 months suggested LAAC (Watchman 39%, Amulet 61%) was noninferior with respect to a composite endpoint. Up to a third of bleeding in the LAAC arm was procedure-related. The current study reports data out to a median of 3.5 years, and shows continued noninferiority, although the reduction in bleeding in the LAAC group is more apparent. Unfortunately because of the COVID pandemic, many of the planned follow-up transoesophageal echocardiograms were cancelled, so we do not have accurate data on the incidence of residual peridevice leaks or device-related thromboses, which can be a problem with LAAC, but the equivalence of clinical events is reassuring. The results are reassuring, but we should await the results of planned much larger studies with long-term follow-up comparing LAAC with DOACs.

Reference: J Am Coll Cardiol 2022;79:1–14
Abstract

Canadian multicenter chronic total occlusion registry

Authors: Strauss BH et al.

Summary: These researchers reported 10-year follow-up for 1624 Canadian registrants with CTOs (chronic total occlusions), stratified according to whether they underwent CTO revascularisation by PCI or CABG, according to routine clinical practice. The 28.2% of patients who underwent early CTO revascularisation (17.5% CABG, 10.7% PCI) were younger and more likely to be male, and generally had fewer comorbidities. Compared with patients who did not undergo CTO revascularisation, those who did had significantly lower 10-year rates of mortality (22.7% vs. 36.6%; adjusted HR 0.67 [95% CI 0.54–0.84]), revascularisation (14.0% vs. 22.8%) and ACS hospitalisation (10.0% vs. 16.6%). The association of CTO revascularisation with lower mortality was particularly robust for CTO revascularisation via CABG in landmark and time-varying analyses (respective HRs 0.56 and 0.60); a marginally significant association was found for PCI in the time-varying analysis (HR 0.711 [95% CI 0.51–0.998]).

Comment: CTOs are found in up to 20% of patients undergoing coronary angiography, but less than one third of patients are revascularised by CABG or PCI. The current study reports long-term follow-up of both surgical and PCI patients entered into the Canadian multicentre CTO registry from April 2008 to July 2009. CTO revascularisation occurred within 3 months of angiography in 28.2% of patients (CABG 17.5%, PCI 10.7%). PCI success rate of CTOs was 71%, and 23% of patients undergoing CABG did not undergo CTO grafting. Medical therapy alone was used in 46.3% of patients. When stratified by specific treatment type in the landmark analysis, only CTO revascularisation by CABG showed significantly lower mortality (HR 0.56); however, in time-varying treatment analysis, CTO revascularisation by either CABG (HR 0.60) or PCI (HR 0.71) showed significantly lower mortality. Whilst nonrandomised with likely selection bias, the data show that CTO revascularisation, particularly with CABG, was associated with improved mortality and less subsequent revascularisation. Randomised trials in this space have been difficult, but in their absence, CTO recanalisation is desirable in appropriately selected patients, particularly if undergoing CABG.

Reference: Circ Cardiovasc Interv 2021;14:e010546
Abstract

Angiographic quantitative flow ratio-guided coronary intervention (FAVOR III China)

Authors: Xu B et al., the FAVOR III China study group

Summary: Adults with stable or unstable angina pectoris or who had experienced an MI ≥72 hours prior to screening, and who had ≥1 stenotic lesion with a diameter of 50–90% in a coronary artery and a reference vessel of ≥2.5mm in diameter, were randomly assigned to PCI guided by QFR (quantitative flow ratio; i.e. when QFR was ≤0.80; n=1913) or an angiography-guided strategy based on standard visual assessment (n=1912). The participants' mean age was 62.7 years, 70.6% were male, 33.9% had diabetes and 63.5% presented with an ACS. Compared with the angiography-guided group, a significantly lower proportion of the QFR-guided group experienced a primary endpoint event (death from any cause, MI or ischaemia-driven revascularisation; 5.8% vs. 8.8%; HR 0.65 [95% CI 0.51–0.83]), with MIs and ischaemia-driven revascularisations the main contributors to the difference.

Comment: Whilst an invasive wire-based assessment of flow-limiting lesions to guide PCI is superior to angiographic guidance, there have been no randomised trials comparing noninvasively determined measures of FFR. The current blinded, randomised, sham-controlled multicentre study from China used the novel QFR, which is derived from three dimensional coronary artery reconstruction and fluid dynamics computation from the angiogram. This enables an estimation of FFR without the use of a pressure wire and hyperaemic agents. After angiography in two projections, the data were transmitted off site to the Angioplus system (Pulse Medical Imaging technology, China), which performed the analysis and returned results to the operator within 10 minutes. A QFR-guided strategy led to fewer stents, less contrast use, shorter procedures and less radiation for the patient. Most importantly, a QFR-guided strategy was superior to standard angiographic guidance with respect to 1-year major adverse cardiac events. Given the underutilisation of invasive pressure wire assessment of intermediate lesions, it is possible that such software could be incorporated into the workflows of all cath labs in the future to improve patient outcomes.

Reference: Lancet 2021;398:2149–59
Abstract

Estimating the economic impacts of percutaneous coronary intervention in Australia

Authors: Lee P et al.

Summary: This registry-based cost burden study used a direct per-person approach to calculate costs of PCI in Victoria, Australia across a variety of indications from a healthcare system perspective, and key drivers of cost were identified. Data from 20,345 consecutive PCIs entered in the VCOR (Victorian Cardiac Outcomes Registry) during 2014–2017 were linked with the Victorian Admitted Episodes Dataset, and key cost drivers were evaluated using generalised linear regression modelling. Procedural complexity, patient length of stay and vascular access site were among the key cost drivers identified. Although there was an increase in total procedural cost over the 2014–2017 period (from $A55,569,740 to $72,179,656), there was no change in mean procedural costs over this time after adjustments for confounding factors (from $12,521 to $12,185). Adjusted mean procedural costs also did not differ notably across PCI indications, ranging from $9872 for unstable angina to $15,930 for ST-segment elevation **MI**.

Comment: CV disease is a major cause of morbidity and mortality in Australia and drives a large amount of healthcare expenditure ($11.8 billion in 2018–2019). An estimated 45,000 PCIs were performed in Australia in 2017–2018. This study used a linked dataset of public patients enrolled in the VCOR and an admitted patient dataset to estimate the cost burden of PCI in Australia. The authors found that overall costs went up, due to increased activity, but the per procedure costs remained largely the same ($12,185 in 2017). This occurred despite more recent patients having a higher baseline risk and undergoing more complex interventions. This was offset largely by a reduced length of stay, which was facilitated by a higher use of radial access (68.5% in 2017 vs. 42.7% in 2014). Given the large costs to the system, it is important we continue to develop models of care using evidence based medicine to optimise patient outcomes.

Reference: BMJ Open 2021;11:e053305
Abstract

Frequency and outcomes of periprocedural MI in patients with chronic coronary syndromes undergoing PCI

Authors: Ueki Y et al.

Summary: The frequency and impact of periprocedural MI was assessed for various definitions among 4404 patients who had undergone PCI for CCS between 2010 and 2018. The proportions of patients meeting the definitions of MI according to the third and fourth UDMI (Universal Definition of Myocardial Infarction), ARC-2 (Academic Research Consortium-2) and SCAI (Society for Cardiovascular Angiography and Interventions) criteria based on high-sensitivity troponin level were 18.0%, 14.9%, 2.0% and 2.0%, and the 1-year cardiac-related mortality rates for patients meeting these respective MI definitions were 2.9%, 3.0%, 5.8% and 10.0%, with ARC-2 and SCAI more relevant for this endpoint than the third and fourth UDMIs (respective HRs 3.90 and 7.66 vs. 1.76 and 1.93).

Comment: Traditionally nonfatal MI has been included in endpoints evaluating new therapies, as it is predictive of subsequent CV-related mortality. With the availability of high-sensitivity troponin tests. There are now several different definitions of periprocedural MI after PCI. The current single-centre study from Bern looked at patients with CCS, and examined the incidence and prognosis of the varying definitions in common use. Levels of high-sensitivity cardiac troponin were determined at baseline and at least once 4–6 hours post-PCI (repeated 6–8 hourly until peaked if elevated). All definitions were associated with CV-related death at 1 year, with HRs from 1.76 for the least restrictive to 7.66 for the most restrictive SCAI definition. Briefly, SCAI defines MI as elevation in cardiac troponin level to ≥70 times the upper limit of normal, or ≥35 times the upper limit of normal with ECG changes. It is important future clinical studies are consistent as to whether we want sensitivity or specificity in terms of definitions of periprocedural MI. In the meantime, there may be value in documenting these events to identify patients at increased risk to ensure optimal medical therapy and follow-up.

Reference: J Am Coll Cardiol 2022;79:513–26
Abstract