WACARDIOLOGY

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TOP 10 CARDIOLOGY TRIALS 2019

1) ISCHAEMIA

This 100 million dollar trial sponsored by the NHLBI is touted as the trial of the decade/century. It randomised 5179 participants followed for 3.3 years with moderate/severe ischaemia to receive initial invasive strategy (angiography followed by stent/CABG) versus optimal medical therapy. A CT scan was performed prior to enrolment to exclude those with left main disease >50% or no significant coronary artery disease. The trial excluded patients with eGFR <30, recent MI, EF <35% or unacceptable angina.

There was no difference in the primary composite endpoint of CV death, non-fatal MI, resuscitated cardiac arrest, hospitalisation for unstable angina or HF. Procedural MI was increased which was offset by a reduction in spontaneous MI in the invasive arm. At 6 months, there was an absolute difference of 1.9% favouring the conservative strategy but at 3.3 years, the absolute difference of 2.2% favoured invasive strategy due to this reduction in spontaneous MI. There was low all-cause mortality in both groups and very low rates of procedural related strokes/death. Quality of life was better in the interventional group.

Some of the controversies of the trial included a change in the primary endpoint during enrolment, a 25% cross-over rate with the medical therapy arm receiving invasive treatment and the inclusion of positive EST (about 25% after the commencement of the trial due to poor recruitment). 34% had no angina. It was also an unblinded trial and no sham procedure. This trial does not apply to acute coronary syndrome patients.

Overall, this is a well done trial that is likely to change practice. There may be less stress testing to assess burden of ischaemia and more use of CTCAs to rule out left main disease. It will also be interesting to see the results of the longer term follow-up to see if that reduction in spontaneous MI with revascularisation will confer longer term benefits.

2) COMPLETE

The question in STEMI has always been what to do when you open the culprit and see other disease. The COMPLETE trial was designed to answer this question. It randomised 4000 patients at 140 centres to complete revascularisation versus medical management. About 2/3 of those patients had the revascularisation on the first day and about 1/3 had the procedure at about 23 days. Only 4% crossed over. The primary outcome of death from CV disease or new MI was 7.8% in the complete revascularisation group vs 10.5% in the culprit-only group. The benefit was driven largely by a reduction in new MI.

The benefit seen in this trial compared to the ISCHAEMIA trial may be because the other significant plaques may be more vulnerable and at higher risk of plaque rupture.

3) DAPA – HF

This trial is a game changer and likely to change practice for heart failure. In this large 4744 patient trial, patients with NYHA Class II-IV heart failure and EF <40% were randomised to dapagliflozin 10mg vs placebo. Over a period of 18 months, the primary outcome of worsening heart failure or CV death occurred in 16.3% of the dapagliflozin group

vs 21.2% in the placebo group. Death from CV cause was reduced by 18%. The benefit was seen in both diabetics and non-diabetics. There was no increase in adverse events such as renal dysfunction or hypoglycaemia.

4) **PARTNER 3 AND EVOLUT**

Two large trials of low risk patients undergoing transcatheter aortic valve replacement (TAVR) showed benefit of TAVR to surgery. The PARTNER 3 used the Edwards balloon expandable valve and the EVOLUT used the self-expandable Medtronic valve. In the PARTNER 3 trial, there was a significant reduction in stroke, all-cause mortality and rehospitalisation at 1 year (driven by a reduction in stroke and mortality). In the EVOLUT trial, there was a reduction in stroke and all-cause mortality (driven by a reduction in stroke).

These two trials are unlikely to change management at this stage, especially in younger, healthier patients as both these trials had very short follow-up and the durability of TAVR valves are still uncertain. The significant pacemaker rates with the self-expandable valve is also a concern.

5) REDUCE-IT

Vascepa, which is concentrated EPA (eicosapentaenoic acid), has now been approved by the FDA for treatment of patients with established cardiovascular disease or with diabetes and other risk factors, with fasting Tg level of 1.52 to 5.63. In the REDUCE-IT trial, a total of 8179 patients were followed for a median of 4.9 years. The primary endpoint of CV death, nonfatal MI, nonfatal stroke, coronary revascularisation or unstable angina occurred in 17.2% in the EPA group vs 22% in the placebo group. CV death was reduced by 20%. AF was more common in the treatment arm with slightly higher rates of bleeding.

When this drug becomes available in Australia, we will likely prescribe it to reduce ischaemic events and CV death.

6) AUGUSTUS

There are now a number of trials, including meta-analysis of patients with AF needing antiplatelets (e.g. post stenting or after ACS). What all these trials have shown (including PIONEER and RE-DUAL PCI) and now AUGUSTUS using Apixaban is that taking away aspirin reduces the risk of bleeding compared to triple therapy (Dual antiplatelet and an anticoagulant). The meta-analysis has also shown that the risk of death, MI and stroke is no different when aspirin is ceased.

7) TWILIGHT

On a similar note, there is a trial asking the question whether dropping aspirin after percutaneous coronary intervention is safe. In this 7200 patient trial, they randomised patients to aspirin and ticagrelor versus ticagrelor alone 3 months after PCI and dual antiplatelet therapy. Not surprisingly, there was a significant reduction in bleeding in those who dropped aspirin after 3 months and no price to pay in terms of death, non-fatal MI or stroke. This trial is likely to change practice in that in those at high-risk of bleeding with high-ischaemic risk, it is safe to drop aspirin after 3 months. The result only applies to ticagrelor. What we do after 12 months is still debated and the use of risk calculators may be needed in the future to make an individualised decision.

Similarly STOPDAPT-2 randomised 3000 patients after drug-eluting stents to either clopidogrel or clopidogrel plus aspirin after 1 month. Clopidogrel monotherapy was superior in terms of reduction in major bleeding events and non-inferior in terms of CV death, MI, definite stent thrombosis and stroke.

SMART-CHOICE randomised 3000 patients with recent drug eluting stents to clopidogrel monotherapy after 3 months vs dual therapy with aspirin and found a similar finding.

8) ISAR-REACT 5

This is an interesting trial which is non-industry funded comparing the use of prasugrel vs ticagrelor in ACS patients for whom invasive treatment is planned. Ticagrelor use is the standard of practice worldwide because of the all-

inclusive PLATO trial and the mortality benefit compared to clopidogrel. This large 4000 patient trial showed that prasugrel significantly reduced the primary endpoint of death, MI or stroke (largely driven by death and MI). Major bleeding was no different.

Whether this will change practice in Perth is uncertain. Prasugrel is certainly more complicated to prescribe with certain contraindications (e.g. Age >75, weight <60kg and previous stroke). It is likely to improve compliance being a once a day drug.

9) RACE 7 ACWAS

This small trial of over 400 patients comparing early cardioversion for recent onset AF to a wait and see approach teaches us a lot about AF. The presence of sinus rhythm in 4 weeks occurred in 91% of the delayed group vs 94% of the early cardioversion group. The key finding is that the majority of patients in the delayed-cardioversion group cardioverted spontaneously within 48 hours. This means that most patients we cardiovert in ED could be spared an anaesthetic and shock if given a chance.

10) COLCOT

This trial looks at the use of colchicine to reduce ischaemic events. It randomised 4745 patients to low dose colchicine 0.5ug once a day within 30 days of a MI, followed for 23 months. The primary endpoint of death from CV causes, MI, stroke, urgent hospitalisation for angina leading to revascularisation was significantly reduced (largely driven by the reduction in MI, stroke and hospitalisation for angina). Diarrhoea and pneumonia was slightly higher in the treatment arm.

This trial is likely to change management. Colchicine is a relatively cheap drug with few side-effects. It gives us a new target for treatment by targeting the inflammatory pathway (see CANTOS trial).

OTHER TRIALS WORTH NOTING

- **PARAGON-HF –** No benefit of saccubutril/valsartan (entresto) for diastolic heart failure
- **DECLARE-TIMI 58 –** Dapagliflozin in type 2 DM and high CV risk improved glycaemic control and reduced HF hospitalisation. Kidney function is better preserved on the SGLT2 antagonist.
- **RECOVERY –** Small trial of very severe asymptomatic aortic stenosis found the incidence of operative mortality and death from CV causes to be lower in those undergoing early AVR than those receiving conservative care.
- **ORION 9 AND 10 –** Inclisiran (the future of CV medicine with injectable oligonucleoides to stop production of PCSK9 protein production by the liver) significantly reduces LDL when given every 6 months as a SC injection and is very safe (safety profile similar to placebo).
- **COMPASS PCI –** Showed similar benefit of low dose rivaroxaban and aspirin in those with stable coronary artery disease and in those who have had stenting.
- **GALILEO –** Low dose rivaroxaban 10mg after TAVR was associated with higher risk of death or thromboembolic complications and a higher risk of bleeding than an antiplatelet strategy.
- **ALCOHOL AF –** Small trial of 140 patients consuming at least 10 drinks a week showed that abstinence (regular urine testing) was associated with significant reduction of recurrent AF as detected by the Kardia mobile device and mean AF burden. BMI and BP also dropped in the abstinence group.
- **ISCHAEMIA-CKD –** Ran concurrently with the ISCHAEMIA trial and showed that invasive approach was not associated with a reduction in CV death or MI. Death or dialysis was 48% higher in the invasive group and stroke nearly 4 fold higher.
- **EXCEL –** 5 year data showed PCI non-inferior to CABG in patients with left main disease amendable to PCI. There were controversies related to the definition of periprocedural MI in those having CABG which drove the non-inferiority endpoint. Death was higher in the PCI arm.

- **GALACTIC –** No survival gain or acute heart failure rehospitalisation at 6 months from aggressive vasodilator therapy in 788 patients randomised. Those in the treatment arm had sublingual or oral nitrates, transdermal nitrates, low dose hydralazine, ACE/AII/ARNI to get BP target to 90-110. Length of hospital stay rate of dyspnoea improvement or reductions in BNP did not differ.
- **PIONEER HF –** 881 patients with decompensated acute heart failure with reduced EF randomised to Entresto or enalapril led to a greater reduction in the NT-proBNP.
- **HYGIA –** In this 19000 RCT, taking the BP tablets at night as opposed to upon wakening reduced the primary endpoint of CV death, heart failure, MI, stroke or coronary revascularisation by 45%. All of the individual primary endpoints were reduced. Medial follow-up of 6.3 years.
- **Apple Watch** – In a large scale study of more than 419,000 Apple watch users, the device accurately detected AF in more than 1/3 of the participants who received notifications of an irregular pulse.
- **Familial Hypercholesterolaemia** - A long-term study of children with FH showed statin therapy beginning at a young age can reduce the incidence of CV events from 26% to 1% at age 39 and reduce death from CV causes from 7 to 1%.

ASPIRIN FOR PRIMARY PREVENTION

Three large studies published in 2019 showed minimal benefit with aspirin and potentially greater harm:

1) **ARRIVE** – In 12546 moderate risk patients, there was minimal reduction in the primary endpoint of first recurrence of MI, unstable angina, stroke or CV death (4.29% vs 4.48% over 60 months - not statistically significant). There was a significant increase in mild GI bleed (0.97% vs 0.46%).
2) **ASCEND** – 15480 patients with diabetes randomised to aspirin followed for 7.4 years. There was a slight reduction in first serious vascular event (8.5% vs 9.6% - statistically significant). Major bleeding occurred in 4.1% vs 3.2% with most of the bleeding being gastrointestinal.
3) **ASPREE** – 19114 patients over 70 years of age with no known CVD showed higher all-cause mortality in the aspirin group due to cancer related deaths. There was modest reduction in CVD risk outweighed by increased bleeding hazard. Those in the highest third of CVD risk however experienced lower CVD event rates with similar rates of bleeding. The reduction in CVD did not translate into improved disability free survival (defined as dementia, permanent physical disability or death).

The American guidelines have given aspirin a class IIb recommendation for aspirin for primary prevention and the European guidelines no longer recommend aspirin.

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