WACARDIOLOGY

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TOP 10 CARDIOLOGY DEVELOPMENTS IN 2016

1) **EMPA-REG –** The FDA has just approved empagliflozin to reduce cardiovascular (CV) death in patients with type 2 diabetes and known CV disease. This is based on the EMPA-REG trial randomising 7020 patients to one of three treatment arms (10mg, 25mg or placebo). The study found a 38% reduction in CV mortality, a 32% reduction in overall mortality and a 35% reduction in hospitalisation for congestive cardiac failure (CCF). The mechanism by which empagliflozin provides these cardiovascular benefit remains uncertain.

   The trial excluded patients with an estimated glomerular filtration rate (eGFR) <30. I would restrict the use of this drug to patients with an eGFR >45. Some patients have developed acute renal failure when started on Empagliflozin. This is uncommon and more likely to occur in patients who are at higher risk of dehydration. One may consider reducing the diuretic dose or initiating a dose of 5mg in those at higher risk. In the long term, patients on Empagliflozin actually experience improvements in renal function. There is also an increased risk of UTIs and rarely, normal BSL ketoacidosis.

   In this trial A1c reduction and cardiovascular system (CVS) outcomes were similar in those who received the 25mg dose vs 10mg dose. SGLT2 inhibitors are better in reducing HbA1c than DPP4 or sulphonylureas and better in reducing BP compared to metformin. Weight loss is achieved with SGLT2 inhibitors.

   LEADER TRIAL – In similar developments, Liraglutide (GLP1 agonist) was tested in 9340 type 2 DM patients at high risk for CV disease with a HbA1c > 7.0. The median follow-up was 3.8 years. 81% had CV disease, 25% had stage 3 or greater chronic kidney disease (CKD). Major adverse cardiac events (MACE), the primary endpoint, was reduced by 13%. Death from CV cause reduced by 22% and there was also a lower incidence of nonfatal myocardial infarct (MI) or cerebrovascular accident. Other trials have shown that the average weight loss with liraglutide is 11.7 pounds after 1 year.

2) **DANISH –** Implantable cardiac defibrillator (ICD) implantation is a class 1 indication for patients with severe left ventricular (LV) impairment for primary prevention. The evidence is much weaker in patients with non-ischaemic cardiomyopathy (CM). The DANISH trial randomised 1116 stable patients with non-ischaemic CM to an ICD. After a median follow-up of over 5 years, the incidence of all-cause mortality was equivalent in both groups. Sudden death was reduced by 50% in the ICD arm (4.3% vs 8.2%). Patients younger than 68 years of age had a significant reduction in all-cause mortality.
   What this trial highlights is the importance of accessing patients' comorbidities when implanting an ICD for primary prevention of sudden cardiac death (SCD) in non-ischaemic

CM, with age being an important factor in the decision making. It also confirms what we have always known – that SCD in non-ischaemic CM is a lot lower compared to patients with ischaemic CM.

3) **PIONEER AF –** In Pioneer AF, 2124 stented patients with AF were randomised to 3 groups.
   - Group 1: Rivaroxaban 15mg + P2Y12 for 12 months
   - Group 2: Rivaroxaban 2.5mg BD plus dual antiplatelet therapy (DAPT)
   - Group 3: Warfarin plus DAPT

   The primary outcome, the incidence of thrombolysis in myocardial infarction (TIMI) minor or major bleeding occurred in 16.8% in group 1, vs 18% group 2 vs 26.7% in group 3. Major bleeding occurred in 2.1% group 1, vs 1.9% group 2, vs 3.3% group 3. It was not powered to look for hard clinical endpoints but MACE was equivalent in all 3 groups. All cause death or recurrent hospitalisation was greater in group 3.

4) **SAVE –** More than 3 years of continuous positive airway pressure (CPAP) did not reduce CV risk more than usual care among patients with CV disease and moderate to severe obstructive sleep apnoea (OSA) in a randomised multicentre trial of 2717 patients. Only 42% of those assigned to CPAP had good adherence. There was no difference in the primary endpoint, a composite of death from any CV cause, MI, stroke or hospitalisation for heart failure. Treatment with CPAP did improve sleepiness, productivity and quality of life was enhanced.
   It was not clear why CPAP treatment did not improve CV outcomes given the strong association seen with other epidemiological studies. More research is likely needed.

   SERVE-HF – On a similar note, treatment of heart failure and reduced ejection fraction (HFREF) with servo-adaptive ventilation to suppress central sleep apnoea/Cheyne-stokes breathing increases all-cause mortality and CVS mortality in a randomised trial of 1300 patients. It is now felt that Cheyne-stokes is a physiological response to heart failure and is not to be suppressed.

5) **ASSERT-2 –** In ASSERT, we found out that in patients over 65 with a pacemaker and hypertension, approximately 1/3 of patients had subclinical atrial fibrillation (AF) over 3 years. Having 6 minutes of AF increases the risk of stroke/systemic embolism by 2.5 fold.

   In ASSERT 2, 256 patients over 65 with a CHADSVASC >=2 OR underlying OSA OR a BMI >30 AND an enlarged atria were implanted with an implantable loop recorder. Subclinical AF of at least 5 minutes was detected in 34% of patients within a year. Whether treating these patients with subclinical AF to prevent embolic events has not been answered and will hopefully be answered by 2 upcoming trials (NOAH and ARTESIA).

6) **ART –** Mammary grafts are known to last longer than saphenous vein grafts (SVG). This trial randomised >3000 patients to bilateral vs unilateral mammary grafts. No significant differences in major CV outcomes were found over 5 years but the incidence of sternal wound complications was significantly higher for bilateral mammary grafts. We will await the result of this trial at the end of 10 years to see if there is a divergence of events.

7) **PARTNER 2A –** This trial randomised 2032 patients at an intermediate risk for surgery to undergo transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR). The primary outcome of all cause death and disabling stroke was similar at the end of 2 years (favours TAVR if transfemoral approach used which is now the preferred approach for the majority of patients). Overall, surgery was associated with less vascular complications and paravalvular regurgitation but more kidney injury, severe bleeding and new-onset AF. TAVR also appeared to improve valve area more than surgery but questions still remain about the durability of TAVR vs SAVR.

8) **HOPE 3 –** This is a large 12705 patient trial with moderate risk of CV disease (men age 55 or female age 65 with one additional CV risk factor including family history, elevated waist hip ratio, etc) randomised to receive rosuvastatin 10mg and or candesartan HCT in a 2x2 factorial trial. The primary endpoint of death from CV cause, nonfatal MI or stroke occurred in 3.7% in the rosuvastatin arm over 5.6 years (a 26% reduction). The combined rosuvastatin and candesartan arm had a 3.5% incidence (30% reduction) and candesartan alone was no different to placebo. This trial points to a more simplified approach with emphasis on the use of statins in intermediate risk patients.

9) **ENSURE-AF –** Found that edoxaban was equivalent to warfarin to the prevention of stroke around the time of electrical cardioversion. All NOACs are now shown to be safe as compared to warfarin for electrical cardioversion.

10) **ATHENA AF –** High dose spironolactone 100mg in a small randomised trial of 360 patients with acute heart failure showed no benefit in the change of NT-ProBNP after 96hrs. There was also no difference in symptoms, urine output, weight changes or clinical events.

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