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RECENT LANDMARK TRIALS IN CARDIOLOGY

Dr. Ravi Vishnu Prasad Additional Professor, Department of Cardiology, IGIMS, Patna

Dr. Akanksha Sinha* Senior Resident, Department of Cardiology, IGIMS, Patna *Corresponding Author

Dr. Sudhir Kumar Assistant Professor, Department of Gastroenterology, AIIMS Patna

ABSTRACT

Cardiology is an ever-evolving medical specialty, impacting a large proportion of human population. In this era of evidence-based medicine, trials and studies form an important cornerstone of clinical practice. Over the period of last few years, numerous clinical trials with valuable contributions to cardiology have been published or presented at major international conferences. This review article aims to summarise the recent important trials and reflect on their clinical context.

INTRODUCTION:

Numerous prominent clinical trials leading to significant advances in the field of cardiology were published or presented at major international conferences in 2021 and 2022. This review aims to summarise these trials and reflect on their clinical context.

Review of Trials:

The past few years have been momentous for the class of SGLT2 inhibitors. There are currently few options for effective, evidence-based therapy in heart failure with preserved EF (HFpEF). The EMPEROR-Preserved trial[1] (Empagliflozin Outcome trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction) examined HFpEF patients with and without diabetes. 5988 patients with NYHA class II–IV heart failure and an LVEF greater than 40% received either empagliflozin vs. placebo. Over a follow-up period of just over 2 years, the primary composite endpoint of CV death or hospitalisation for heart failure occurred in 13.8% in the empagliflozin group and 17.1% in the placebo group (HR 0.79, 95% CI 0.69–0.90; p <0.001). This effect was largely driven by the reduction in HF hospitalisations.

The DELIVER [2](Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction) study randomised 6263 symptomatically stable patients with HF and LVEF>40% to dapagliflozin versus placebo. Dapagliflozin was associated with an 18% reduction in the primary endpoint of death or worsening HF (16.4% vs. 19.5%; HR 0.82, 95% CI 0.73–0.92; P<0.001). Benefit was primarily driven by a reduction in HF hospitalizations, not mortality.

The EMPULSE [3](Empagliflozin in Patients Hospitalized for Acute Heart Failure) trial randomised 530 acutely decompensated patients hospitalised with heart failure, regardless of ejection fraction or diabetic status to Empagliflozin versus placebo. Those with IV vasodilators, IV inotropes, requiring increasing IV diuretic doses, cardiogenic shock or recent ACS were excluded. Empagliflozin versus placebo was more frequently associated with clinical benefit in the primary composite endpoint of death, number of HF events, time to first HF event, and change in Kansas City Cardiomyopathy Questionnaire-Total Symptom Score at 90 days (stratified win ratio 1.36; 95% CI 1.09–1.68; P = 0.0054).

Sacubitril/ valsartan has been an important addition to the treatment of patients with HFrEF in recent years. PARADISE-MI [4](Prospective ARNI vs. ACE inhibitor trial to Determine Superiority in reducing heart failure Events after Myocardial Infarction examined the use of sacubitril/valsartan in 5661 patients with an acute MI complicated by reduced ejection fraction (<40%) and/or pulmonary congestion with 2830 patients randomised to receive sacubitril/valsartan while the remaining 2831 received ramipril. The composite endpoint of CV death or HF event occurred in 338 (11.9%) of the sacubitril/valsartan group and 373 (13.2%) of the ramipril group (HR 0.90, 95% CI 0.78–1.04; p = 0.17). This suggests that further work is required to identify whether there is a subgroup of patients that may benefit from this drug in the acute period following an MI.

Recently, several major trials studied whether shortened dual antiplatelet therapy (DAPT) reduced bleeding risk without increasing risk of further ischaemic events. The MASTER DAPT[5] study (Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk) randomly assigned 4434 patients at high bleeding risk (HBR) to 1 month DAPT (abbreviated therapy) vs. ongoing DAPT for at least 3 months (standard therapy). PCI was undertaken with a biodegradable-polymer sirolimus-eluting stent in all patients. Abbreviated vs. standard therapy met non-inferiority for the primary outcomes of net adverse clinical events (NACE; death, MI, stroke or major bleeding) (p <0.001) and MACE (death, MI or stroke) (p = 0.001) at 335 days. Having met non-inferiority, further analysis showed the abbreviated strategy was associated with significant reduction in major or clinically relevant non-major bleeding (6.5% vs. 9.4; p superiority <0.001).

Complete revascularisation has been found superior to culprit lesion only PCI in STEMI, with increasing evidence for multivessel PCI either acutely, during initial hospitalisation or within 45 days, but it is unclear if guiding the complete revascularisation by fractional flow reserve (FFR) is superior to angiography only guidance. In the multicentre FLOWER-MI study [6](FLOW Evaluation to Guide Revascularization in Multi-Vessel ST-Elevation Myocardial Infarction), 1171 patients with STEMI, with successful PCI to the culprit artery, were randomised to FFR (n = 590) vs. angiography only (n = 581) guided complete revascularisation. The primary outcome of death, myocardial infarction (MI) and unplanned hospitalization leading to urgent revascularisations at 1 year was not found to be significantly different for FFR vs. angiography-only guidance (5.5 vs. 4.2%; HR 1.32 95% CI 0.78–2.23]; p = 0.31), although given the wide confidence intervals, the findings are not conclusive.

The FLAVOUR [7](Fractional Flow Reserve and Intravascular Ultrasound-Guided Intervention Strategy For Clinical Outcomes in Patients With Intermediate Stenosis) trial seeked to evaluate fractional flow reserve (FFR) compared with intravascular ultrasound (IVUS) among patients with an

intermediate coronary stenosis. The primary outcome, all-cause death, myocardial infarction, or revascularization at 24 months, occurred in 8.1% of the FFR group vs. 8.5% of the IVUS group (p for noninferiority = 0.015). This trial showed that among patients with an intermediate coronary stenosis, FFR-guided PCI was noninferior to IVUS-guided PCI.

The LAAOS III [8](Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke Study III) evaluated the efficacy and safety of concomitant left atrial appendage (LAA) occlusion vs. no occlusion in patients in atrial fibrillation and a CHAD2DS2-Vasc score ≥2 undergoing cardiac surgery, of whom 36% had a mitral valve procedure. The trial showed a reduction of the risk of stroke or systemic embolic event [4.8 vs. 7.0%, HR = 0.67 (0.53–0.85), *P* = 0.0010] in those with LAA occlusion. OAC usage rates at 3 years were similar between groups (75% vs. 78%) with no significant difference in bleeding between groups noted. Although not suggestive that LAAO is a replacement to OAC, it does highlight a segmented benefit in stroke risk reduction when added to OAC.

The EARLY-AF [9](Early Aggressive Invasive Intervention for Atrial Fibrillation) trial randomised patients with paroxysmal atrial fibrillation to cryoballoon ablation vs antiarrhythmic drug therapy. Among patients with paroxysmal atrial fibrillation, an initial strategy of catheter cryoballoon ablation was beneficial. Catheter cryoballoon ablation compared with antiarrhythmic drug therapy was associated with a lower incidence of persistent atrial fibrillation or recurrent atrial tachyarrhythmia. Catheter cryoballoon ablation was also associated with a reduction in hospitalization compared with antiarrhythmic drug therapy.

The EXPLORER-HCM trial [10](Clinical Study to Evaluate Mavacamten (MYK-461) in Adults With Symptomatic Obstructive Hypertrophic Cardiomyopathy) previously reported that mavacamten, a cardiac myosin inhibitor, led to significant improvements in peak oxygen consumption (pVO2) and NYHA class of symptoms in patients with hypertrophic cardiomyopathy with significant left ventricular outflow tract (LVOT) obstruction. A further analysis of EXPLORER-HCM has now also studied quality of life. A total of 251 patients with symptomatic obstructive hypertrophic cardiomyopathy (gradient C 50 mmHg) and NYHA class II–III symptoms were assigned to mavacamten (n = 123) or placebo (n = 128) for 30 weeks. At 30 weeks, the change in KCCQ-OS (overall summary) score was greater with mavacamten (14.9 [SD 15.8]) than placebo (5.4 [SD 13.7]) (difference+ 9.1, 95% CI 5.5–12.8; p<0.0001) and interestingly the beneficial effect was lost when the drug was stopped. The previous efficacy data and these new quality of life data support use of this drug for this group of patients.

VALOR-HCM [11](Mavacamten in Adults With Symptomatic Obstructive HCM Who Are Eligible for Septal Reduction Therapy) trial randomised 112 patients eligible for septal reduction therapy (SRT) to mavacamten (starting at 5 mg and titrating using LVEF and LVOT gradient) versus placebo. After 16 weeks follow-up, mavacamten was associated with marked reduction in obstructive parameters with only 17.9% still meeting guideline criteria for SRT (vs. 76.8% of placebo patients; 95% CI: 0.44–0.74; P<0.001). The results of this trial indicate that mavacamten improved symptoms and significantly reduced eligibility for needing SRT among symptomatic patients with obstructive HCM who were considering SRT.

In the REVIVED-BCIS2 [12](REVascularisation for Ischaemic Ventricular Dysfunction) trial, 700 patients with left ventricular ejection fraction (LVEF) ≤ 35% and extensive coronary artery disease, as defined by the British Cardiovascular Intervention Society (BCIS) jeopardy score, were randomised to PCI or optimal medical therapy (OMT). Over a median followup time of 3.4 years, PCI did not result reduction in the primary composite outcome of death or hospitalization for heart failure when compared to OMT alone [37.2% vs. 38.0%; HR 0.99; 95% confidence interval (CI), 0.78–1.27; P = 0.96].

CONCLUSION:

This paper has highlighted and summarised the key cardiology trials that were published in the last few years. Many will guide clinical practice and influence guideline development.

REFERENCES:

1. Anker SD et al; EMPEROR-Preserved Trial Investigators. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. N Engl J Med. 2021 Oct 14;385(16):1451-1461.
2. Solomon SD et al; DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022 Sep 22;387(12):1089-1098.
3. Voors AA et al; The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med. 2022 Mar;28(3):568-574.
4. Pfeffer MA et al; PARADISE-MI Investigators and Committees. Angiotensin Receptor-Neprilysin Inhibition in Acute Myocardial Infarction. N Engl J Med. 2021 Nov 11;385(20):1845-1855.
5. Valgimigli M et al; MASTER DAPT Investigators. Dual Antiplatelet Therapy after PCI in Patients at High Bleeding Risk. N Engl J Med. 2021 Oct 28;385(18):1643-1655.
6. Puymirat E et al; FLOWER-MI Study Investigators. Multivessel PCI Guided by FFR or Angiography for Myocardial Infarction. N Engl J Med. 2021 Jul 22;385(4):297-308.
7. Koo BK et al; FLAVOUR Investigators. Fractional Flow Reserve or Intravascular Ultrasonography to Guide PCI. N Engl J Med. 2022 Sep 1;387(9):779-789.
8. Whitlock RP et al; LAAOS III Investigators. Left Atrial Appendage Occlusion during Cardiac Surgery to Prevent Stroke. N Engl J Med. 2021 Jun 3;384(22):2081-2091.
9. Andrade JG et al; EARLY-AF Investigators. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. N Engl J Med. 2021 Jan 28;384(4):305-315.
10. Olivotto I et al; Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2020 Sep 12;396(10253):759-769.
11. Desai MY et al; Myosin Inhibition in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy. J Am Coll Cardiol. 2022 Jul 12;80(2):95-108.
12. Perera D et al; REVIVED-BCIS2 Investigators. Percutaneous Revascularization for Ischemic Left Ventricular Dysfunction. N Engl J Med. 2022 Oct 13;387(15):1351-1360.