Field of cardiology has undergone a paradigm shift over the last decade, from the use of bare metal stents to bio-absorbable stents and from surgical aortic valve replacement to percutaneous aortic valve in patients with aortic stenosis. Every year new trials are published which provide evidence to change the clinical management of our patients. In the past year, landmark trials which were published are Heart Outcomes Prevention Evaluation-3 (HOPE-3), PARTNER 2, The Systolic Blood Pressure Intervention Trial (SPRINT), ABSORB III, Dual Antiplatelet Therapy trial (DAPT) and PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin - Thrombolysis in Myocardial Infarction 54). In the current review, we will discuss these trials along with their clinical implications and how they have changed our clinical practice.

HOPE-3

It is well established that antihypertensive therapy and statins lowers cardiovascular risk in patients with high risk. However, their role in intermediate-risk patients (annual event rate of less than <1%) without established cardiovascular disease is uncertain. HOPE-3 trial was designed to answer this question. It consisted of more than 12,000 patients with a median follow up period of 5.6 years. It had 2x2 factorial design, hence had three arms – an antihypertensive regimen, a statin and a combination of two.

In first arm, patients received BP-lowering treatment which consisted of candesartan 16 mg/day and hydrochlorothiazide 12.5 mg/day. These patients did not have significantly fewer occurrences of a composite of CV-related death, nonfatal MI, or nonfatal stroke (the first co-primary outcome) at a mean follow up of 5.6 years compared with those who received placebo (4.1% vs 4.4%, respectively). The second co-primary outcome, which was heart failure, cardiac arrest, or revascularization to the composite was also not statistically significantly different between two groups (4.9% vs 5.2%).

In second arm, study participants were randomized to rosuvastatin 10 mg/day vs placebo. A significant reduction in the first coprimary outcome was seen in the rosuvastatin group (P = 0.002) with a 24% lower risk for CV events. Similarly, statistical significance was achieved for second coprimary event also (P<.001).

The trial’s third arm which was combination of two therapy randomized patients to rosuvastatin plus candesartan/hydrochlorothiazide vs rosuvastatin plus placebo vs candesartan/hydrochlorothiazide plus placebo vs two placebos It was seen that those who received both of the treatment drugs together had significantly lower rates of the first primary outcome vs the double-placebo group (3.6% vs 5.0%, respectively, P=0.005), as well as the second primary outcome (4.3% vs 5.9%, P=0.003).

In conclusion, it was seen that in an intermediate-risk population, everybody was benefited with statins and that statins were found to be safe. But in terms of blood-pressure lowering, those without elevated BP do not derive any benefit.

PARTNER 2

Transcatheter aortic valve replacement (TAVR) has become treatment of choice in severe symptomatic aortic stenosis patients with prohibitive surgical risk. In patients with high surgical risk either TAVR or surgical aortic valve replacement is an option. PARTNER 2 assessed the role of TAVR in patients with intermediate surgical risk.

PARTNER 2 randomized 2032 patients with severe symptomatic aortic stenosis who underwent TAVR with the balloon-expandable Sapien XT valve or surgery. The mean age was 81 years at the time of implantation. Patients were considered to be at intermediate risk after clinical assessment by a multidisciplinary heart team. The mean Society of Thoracic Surgeons score was 5.8%, with 81.3% patients had a score between 4% and 8%. At 2 years, the primary composite end point of all-cause death or disabling stroke occurred in 19.3% with TAVR and 21.1% with surgery in the intention-to-treat population (hazard ratio [HR] 0.89; P=0.25). TAVR met the threshold for noninferiority in intention-to-treat (P=0.001) and as-treated analyses (P<0.001).

TAVR is a reasonable alternative to surgical aortic-valve replacement (AVR) in intermediate-risk patients and may be superior when using a transfemoral approach.

SPRINT TRIAL

Latest JNC 8 guidelines recommends treating to a target of 150/90 mm Hg for the patients 60 years of age and older and to 140/90 mm Hg in others. SPRINT compared the effects of antihypertensive treatment with a systolic blood pressure (SBP) target of <120 mm Hg (intensive treatment) versus <140 mm Hg (standard treatment).
It randomized 9361 hypertensive adults ≥50 years of age who had an average SBP of 130–180 mm Hg and were at additional risk for cardiovascular disease (CVD). During follow-up, the mean SBP was 121.5 mm Hg in intensive treatment group and 134.6 mm Hg in standard treatment group. Trial was stopped prematurely after a median follow-up of 3.26 years because primary composite outcome of myocardial infarction, non–myocardial infarction acute coronary syndrome, stroke, acute decompensated heart failure, and CVD death was reduced by ≈ 25% in intensive treatment group. All-cause mortality was also reduced by ≈ 27% in the intensive treatment group. Acute kidney injury or failure were more common in the intensive (4.1%) than in the standard (2.5%) arm. Electrolyte abnormalities were also more common in the intensive (3.1%) than in the standard (2.3%) arm.

Hence SPRINT redefined blood pressure targets and questions J-shaped curve. For people at high cardiovascular risk, a systolic goal of less than 120 mm Hg is appropriate.

**ABSORB III**

Drug-eluting coronary stents (DES) have been associated with better clinical outcomes than bare-metal stents however, there is ongoing risks of stent thrombosis and restenosis. These late adverse events are due to permanent metallic stents. Fully bioresorbable stents i.e. bioresorbable vascular scaffolds (BVS) have been developed which undergo complete bioresorption hence might be devoid of late adverse events.

In ABSORB III trial 2008 patients with stable or unstable angina were randomized in a 2:1 ratio to receive an everolimus-eluting bioresorbable vascular (Absorb) scaffold or an everolimus-eluting cobalt–chromium (Xience) stent. At one year there was no significant difference between the Absorb group and the Xience group in rates of cardiac death, target-vessel myocardial infarction, or ischemia-driven target-lesion revascularization. However, stent thrombosis within 1 year occurred in 1.5% of patients in the Absorb group and in 0.7% of patients in the Xience group (P=0.13) which was numerically higher but statistically not significant.

Hence, ABSORB trial showed non-inferiority of BVS to current generation available DES. But patient and lesion selection criteria which were used in this trial needs to be kept in mind. Similarly increased risk of stent thrombosis is alarming hence effective duration and need of dual antiplatelet therapy in these patients is currently not known.

**DAPT AND PEGASUS-TIMI 54**

Dual antiplatelet therapy (DAPT) is standard treatment for patients with acute coronary syndromes (ACS) and in patients undergoing DES implantation and includes use of aspirin with either an irreversible thienopyridine P2Y12 inhibitor, clopidogrel or prasugrel, or ticagrelor. DAPT study assessed the benefit of extended Post-PCI DAPT in patients with or without acute coronary syndrome. PEGASUS-TIMI 54 examined the effects of long-term DAPT with aspirin and ticagrelor, compared with aspirin alone in patients with prior history of myocardial infarction (MI).

DAPT trial compared continuing thienopyridine therapy for 30 months as opposed to stopping it after 12 months in patients who were already taking aspirin after coronary stenting. About two-thirds of the study patients received clopidogrel, and one-third received prasugrel. Patients who had ischemia or bleeding during the first 12 months were excluded from the 12–30-month study. Continued treatment with thienopyridine, as compared with placebo, reduced the rates of stent thrombosis and major adverse cardiovascular and cerebrovascular events. The rate of myocardial infarction and death from any cause was also lower. The rate of moderate or severe bleeding was increased with continued thienopyridine.

PEGASUS-TIMI 54 trial randomized 21,162 patients who had had a MI 1 to 3 years prior to ticagrelor at a dose of 90 mg twice daily, ticagrelor at a dose of 60 mg twice daily, or placebo. It was seen that over a three year follow up period both ticagrelor doses reduced, as compared with placebo the rate of the primary efficacy end point which was the composite of cardiovascular death, myocardial infarction, or stroke. However, rates of TIMI major bleeding were significantly higher with ticagrelor than with placebo.

Hence above trial results demonstrate that in patients with history of ACS which are at high risk of further ischemic events may benefit from prolonged ticagrelor based DAPT but with slightly increased risk of bleeding. Similarly in patients who had undergone stent implantation extending therapy to 30 months reduced the risk of stent thrombosis and MI but also increased the risk of mild to moderate bleeding in patients with or without prior history of MI.

**CONCLUSION**

To summarize, these recent landmark trials showed benefit of statins in patients without CVD, TAVR emerging as preferred modality for intermediate and high risk severe aortic stenosis, lower BP targets against as recommended by current guidelines, bio-absorbable stents being non-inferior to current generation DES and suggested benefit of extended duration of DAPT therapy in post PCI and ACS patients.

**REFERENCES**


