ABSTRACT
Recently published clinical trials have had impact on the management of patients with hypertension, dyslipidaemia, and patients at high-risk of cardiovascular diseases. This article reviews the relevant trials and the basis for changing clinical practice in the face of evidence-based medicine.

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HYPERTENSION
Epidemiological data showed that lower blood pressure is associated with lower cardiovascular risks. Observational studies have shown that cardiovascular risks begin to increase from blood pressure of 117/75 mmHg. For each 20 mmHg or 10 mmHg increase in systolic or diastolic pressure respectively, mortality from ischaemic heart disease or stroke is doubled. Meta-analysis showed that for every 2 mg reduction is systolic blood pressure, cardiovascular mortality is reduced by 7-10%.

However, generations of physicians have long held the notion that as we age, it is normal and acceptable to have higher blood pressure. Attempts to initiate blood pressure reduction in the very elderly (>80 years) have been met with resistance from both patients and physicians. This is not helped by the fact that most studies have excluded very elderly subjects. The HYVET study was undertaken in very elderly (≥80 years) subjects with hypertension. The average age of enrolled subjects was 83.6 years, with mean blood pressure of 173.0/90.8 mmHg. Subjects in the active treatment group were given the diuretic Indapamide with or without Perindopril (ACE-inhibitor), while the control group received placebo. The trial was terminated early by the Data and Safety Monitoring Board, resulting in a mean follow-up period of 1.8 years. The primary end point was the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalisation for angina, resuscitation after sudden cardiac arrest, and coronary revascularisation.

This trial was also terminated early at mean follow-up of 36 months. Blood pressure reduction was similar in the two groups, but the Benazepril–Amlodipine group had 2.2% fewer events than the Benazepril–Hydrochlorothiazide group, representing a relative risk reduction of 19.6%. With this head-to-head comparison, the Benazepril–Amlodipine combination was therefore shown to be superior to the Benazepril–Hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events. There is now, therefore, an evidence-based preferred combination therapy in the treatment of hypertension.

DYSLIPIDAEMIA
Statins are the drug of choice in the treatment of dyslipidaemia. Clinical trials have proven substantially the benefits on cardiovascular disease reduction in both primary and secondary prevention trials. Major guidelines endorse Statin therapy for the reduction of LDL-cholesterol. However, Statin therapy does not adequately address vascular risks associated with elevated triglyceride & low HDL-cholesterol.

To address this residual risk, combination therapy is often needed in patients with elevated triglycerides or low HDL-cholesterol. Several drugs are available for use in combination with Statins: Fibrates, Niacin, and Ezetimibe.

The ARBITER6-HALTS trial shed some light to what is possibly the preferred combination for such patients. The trial used a surrogate end point of change in carotid artery intima-media thickness. Major adverse cardiovascular events were studied as a secondary end point. In this short trial, extended-release niacin was compared with Ezetimibe when combined with Statin therapy. The result showed that niacin therapy led to regression of carotid intima-media thickness and fewer clinical cardiovascular events. Paradoxically, there was a greater degree of

Bernard WK Kwok, MBBS (S’pore), M.Med (Int.Med), MRCP (UK), FAMS, FACC, Senior Consultant Cardiologist, Mt Elizabeth Medical Centre
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This failure of Ezetimibe to reduce or halt progression of carotid intima-media thickness was also demonstrated in the ENHANCE trial published a year earlier\(^4\). In that trial involving patients with familial hypercholesterolemia, combined therapy with Ezetimibe and Simvastatin did not result in a significant difference in changes in intima-media thickness, as compared with Simvastatin alone, despite decreases in levels of LDL cholesterol.

It would appear that Ezetimibe should not be a favoured second agent for use when combined with Statins. Niacin, which found favour in the 1980’s, should see renewed interest in its use.

Whilst the JUPITER trial is not a study of patients with dyslipidaemia, its study of Rosuvastatin on high-risk patients (defined as having hsCRP ≥ 2 mg/L) was enlightening\(^5\). In the trial, apparently healthy subjects with LDL-cholesterol < 130 mg/dL but hsCRP ≥ 2 mg/L were given Rosuvastatin or placebo. The subjects treated with Rosuvastatin had 44% reduction in the primary composite end point of myocardial infarction, stroke, unstable angina/cardiac revascularisation, cardiovascular death. This has now opened a new arena for the use of Statins in the primary prevention of cardiovascular diseases.

High-Risk Patients

Patients who have vascular disease or diabetes with end-organ damage, are known to be at high risk for cardiovascular diseases. Angiotensin-converting–enzyme (ACE) inhibitors are known to reduce mortality and morbidity in these groups of patients.

The ONTARGET trial compared the ACE inhibitor Ramipril, the Angiotensin Receptor Blocker (ARB) Telmisartan, and the combination of the two drugs in patients with vascular disease or high-risk diabetes\(^6\). This is the largest ARB trial to date in terms of patient-treatment years. Patients were randomised in a double-blind fashion to the two treatment arms. The results showed that the ARB Telmisartan is non-inferior, or as effective as the ACE-inhibitor Ramipril, in reducing cardiovascular events. In addition, Telmisartan was better tolerated, with fewer side-effects. Combination therapy with ACE-inhibitor and ARB resulted in higher rates of adverse events (hypotension, renal dysfunction), but without added cardiovascular protection.

TRANSCEND trial programme, studied the same category of patients but who were unable to tolerate ACE-inhibitors\(^7\). Patients were randomised to Telmisartan or placebo. The results showed that although Telmisartan had no significant effect on the primary outcome, which included hospitalisations for heart failure, it modestly reduced the risk of the composite outcome of cardiovascular death, myocardial infarction, or stroke.

In the ONTARGET trial, Telmisartan is shown to be as cardioprotective as, but better tolerated than, the ACE-inhibitor Ramipril, the previous gold standard. Combination therapy of ACE-inhibitor and ARB, however, confer no added benefits. It is reasonable to conclude that there is no cardiovascular indication for such combination therapy.

In TRANSCEND, we finally have proof that patients who are unable to tolerate ACE-inhibitors now have a clinically-proven alternative that will lower the risk of heart attack and stroke.

**References**


**Learning Points**

- This HYVET study demonstrated that antihypertensive treatment with Indapamide, with or without Perindopril, in persons 80 years of age or older is beneficial.
- Benazepril–Amlodipine combination was shown to be superior to the Benazepril–Hydrochlorothiazide combination in reducing cardiovascular events in patients with hypertension who were at high risk for such events.
- The JUPITER trial has now opened a new arena for the use of Statins in the primary prevention of cardiovascular diseases.
- The ONTARGET trial results showed that the ARB Telmisartan is non-inferior, or as effective as the ACE-inhibitor Ramipril, in reducing cardiovascular events. In addition, Telmisartan was better tolerated, with fewer side-effects.
- The TRANSCEND trial proves that patients who are unable to tolerate ACE-inhibitors now have a clinically-proven alternative that will lower the risk of heart attack and stroke.