INDIAN SOCIETY OF HYPERTENSION
CURRENT MEDICAL CONCEPTS
HTNJ

Review Article

Hypertension Outcome Trials: How Relevant are they in the Real World Practice of Medicine?

S. N. Narasingan[1,2]

[1] Former Adjunct Professor, Lipid Association of India. Dr. MGR Medical University, Chennai, Tamil Nadu, India, [2]SNN Specialities Clinic and SNN Diagnostic Centre, Chennai, Tamil Nadu, India

Abstract

Hypertension is a major risk factor for cardiovascular (CV) morbidity and mortality. The prevalence of hypertension is increasing in alarming proportion in both urban and rural population in India. Benefits of lowering blood pressure (BP) resulted in the reduction of CV risk, including mortality benefit. Randomized control trials conducted in people with hypertension had shown beneficial effects in the treatment group compared to that of the placebo or other comparator drugs. Trials in hypertensive participants have given us lot of information about efficacy and safety of pharmacological agents. Combination therapy has shown more advantages for reaching the BP goals early and for additional benefits of CV outcome. There are some controversial issues about usage of certain drugs and the goals of BP in people with diabetes and chronic kidney disease. However, meta-analysis of various trials gave answers for some issues. This chapter will focus on major hypertension outcome trials and their relevance in the real world practice of medicine.

Key words: Hypertension, CV risk, anti hypertensive drugs

Introduction

Hypertension is the most common condition seen in primary care and leads to myocardial infarction (MI), stroke, renal failure, and heart failure (HF). Atrial fibrillation, peripheral arterial disease, and aortic dissection are not uncommon complications. Death occurs if not detected early and treated appropriately. Hypertension is a major public health challenge globally and affects nearly 26% of the population in India as per the data projected in 2015.[1]

It is not only a silent killer but also a leading risk factor for mortality. There is a huge body of evidence from randomized control trials (RCTs) on hypertension indicating not only the benefit of lowering blood pressure (BP) but also reflecting appreciable benefit in cardiovascular (CV) morbidity and mortality. This chapter will focus on major hypertension outcome trials and their relevance in the real world practice of medicine.

Lessons Learnt from Hypertension Trials

Hypertension treatment recommendations are based on strict interpretation of data only from RCTs which compared placebo and comparator drug. There are good number of RCTs which had used different group of drugs either alone or in combination and compared. These RCTs paved the way for health-care providers to manage hypertension at all stages, including complications with target organ damage. These outcome trials have provided useful and relevant information in people with diabetes, the elderly and with chronic kidney disease (CKD) and cardiovascular disease CVD.

Pharmacotherapy: Renin-Angiotensin Inhibitors

Renin-angiotensin-aldosterone system (RAAS) is active not only in the initial stages of hypertension but also in the progression of hypertension, including clinical CVD and nephropathy. Blocking the RAAS by angiotensin-converting enzyme inhibitors (ACEIs) have shown remarkable improvement in BP control and reduction in CV morbidity and mortality. RCTs conducted using various ACEI have shown beneficial affects in reducing proteinuria with marginal benefit in CV outcome. Ramipril in hope study has proved for its safety and efficacy in the prevention of CV complications. Angiotensin II receptor blockers (ARBs)

Address for correspondence:
S. N. Narasingan, SNN Diagnostic Centre, O# 38, N# 12, New Thandavaraya Street, Chennai, Tamil Nadu - 600021, India.
E-mail : drsnn.sc@gmail.com

Received 8-10-2018; Accepted 10-11-2018

which block AT1 receptors have demonstrated to match with the benefits that are obtained with ACEI. Number of RCTs with ARBs compared with the placebo or other comparator drugs proved to have beneficial effects. ARBs are good in the prevention of stroke events in the general population and diabetics. Although ARBs were linked with a fear of inducing MI in the past, a recent meta-analysis published in BMJ[2] clearly has shown that there is no correlation between ARBs and increase in MI risk. Now, it is clear that ARBs do not induce MI and are considered safe. ARBs are potent drugs to reduce proteinuria and for reducing renal morbidity. Ongoing telmisartan alone and in combination with ramipril global endpoint trial have clearly shown that telmisartan is noninferior to ramipril in bringing down CV hard end-points. However, the study has proved the bad effects of increasing renal morbidity by combining ramipril with telmisartan. Combination of ACEI and ARB is not an ideal choice in any clinical situation, either with diabetes or hypertension and or CKD. Aliskiren trial in Type 2 diabetes using cardio-renal endpoints showed that the addition of direct renin inhibitor aliskiren to background therapy with an ACEI or ARB increases the incidence of hyperkalemia and hypotension while producing no added CV benefit: These results led to a black box Food and Drug Administration (FDA) warning against this form of dual renin-angiotensin system (RAS) blockade.[3-5] Dual RAS blockade either with ACEI + an ARB or with Aliskiren + an ACEI or ARB is now contraindicated.

As monotherapy, ACEIs are generally less effective in lowering BP in Africans and in older patients with low-renin hypertension, but they are quite effective in these groups when combined with a low-dose diuretic or calcium channel blocker (CCB). In meta-analysis, ACEIs are found to be equivalent to CCBs in protecting against coronary events, slightly less effective in protecting against stroke, but better in protecting against HF.[6]

Diuretics

Systolic hypertension in the elderly program (SHEP) and systolic hypertension in Europe study revealed that diabetics derive more benefit from the same degree of BP lowering than those without diabetes. SHEP – long-term follow-up determined whether the effect of BP lowering during SHEP is associated with long-term (22 years) outcomes such as CV and all-cause mortality and extended life expectancy. People on active therapy with chlorthalidone lived an average 516 days longer and 205 days free of all cause mortality, not necessarily CV mortality.[7]

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[8]

This is the largest hypertension trial which recruited nearly 42,418 patients with comorbid conditions, including diabetes. There were 4 arms in the study. Doxazosin arm was stopped because of increase in HF. Chlorthalidone, a good old diuretic, was compared with CCB – Amlodipine and ACEI, lisinopril in this study and all patients were followed up for a period of 5 years. Primary end-point: Fatal coronary heart disease (CHD) and non-fatal MI. Chlorthalidone was found to be equal compared to amlodipine and lisinopril in reducing CV risk. Chlorthalidone was found to be superior when compared to amlodipine and lisinopril in HF, and it was better in the prevention of stroke compared to that of lisinopril.

Chlorthalidone versus Hydrochlorothiazide (HCTZ)

Even though HCTZ has enjoyed widespread use in clinical practice, chlorthalidone is the choice in clinical practice with good evidence from RCTs. Greater effectiveness of chlorthalidone than HCTZ is strongly suggested by *post hoc* analysis of the multiple risk factor intervention trial data[9] which showed better outcomes with chlorthalidone. A small single-center ambulatory BP monitoring (ABPM) study showed a much longer duration of action of chlorthalidone. Loop diuretics are less effective BP-lowering agents and should be reserved for treating hypertension in the setting of advanced CKD (stage 3 or higher). Chlorthalidone may also be effective in patients with Stage 3 CKD. Diuretics enhance the potency of all other classes of antihypertensive agents. Thiazide and thiazide-like diuretics combine, particularly well with ACEIs and ARBs. This combination blunts reactive RAS activation and thus increase antihypertensive efficacy. The current trend is to recommend thiazide-like diuretics such as chlorthalidone and indapamide in the place of hydrochlorothiazide. Multiple RCTs have shown that thiazide-type diuretics reduce coronary events, strokes, and HF in elderly patients.

Hypertension in the Very Elderly Trial (HYVET)[10]

This trial has focused on the treatment of hypertension, in elderly patients >80 years. Before the study publication, we were not very sure of treating octogenarians. This study used diuretic indapamide with ACEI perindopril and compared with the placebo. All end-points, including stroke (hazard ratio [HR]:0.70), stroke-deaths (HR:0.61), all-cause mortality (HR:0.79), CV death (HR:0.77), cardiac death (HR:0.71), and hospitalization for HF (HR:0.36) were reduced considerably compared to that of the placebo. This study emphasizes the role of pharmacotherapy and advantages in reducing CV morbidity and mortality in the elderly. The results of this study will help us to adopt the same measures of controlling HYVET.

Importance of Home BP Monitoring (HBPM) and ABPM

The 2011 U.K. guidelines from the National Institute of Clinical Excellence (NICE) and the 2013 European Society of Hypertension/European Society of Cardiology guidelines place far greater emphasis than U.S. guidelines on home and ABPM for clinical decision-making.[11-13] Based on registry data from the 11-country International database on ambulatory BP in relation to CV outcomes ambulatory and HBPM should be routine in hypertension. Masked (out-of-office only) hypertension

is so common in older adults and in people with diabetes. Conventional office BP readings alone will promote either over treatment or under treatment of hypertension.

Role of Beta Blockers

Beta-blockers in the management of hypertension are still debated. Lindholm *et al.* published a meta-analysis which revealed that atenolol-based anti-hypertensive therapy increased the incidence of stroke by 16% and precipitated new-onset diabetes. Beta blocker like atenolol has to be avoided in managing hypertension . However , non -atenolol based betablockers have a role in managing hypertension. This is more relevant in people with diabetes because of adverse metabolic effects and alteration in the lipid profile. NICE guidelines in 2011, pushed beta-blockers as a last resort in the management of hypertension. In view of the adverse effects such as increase in stroke and new-onset diabetes, beta-blockers do not enjoy the first place in the management of hypertension. There is a definite role for usage of vasodilating beta-blockers other than atenolol, particularly for secondary prevention. Hence, the current role of beta-blockers is in situations such as arrhythmias, increased sympathetic activity, coronary artery disease (CAD), and congestive HF complicated by hypertension.[14] Vasodilating beta-blockers are much more potent antihypertensive agents. They do not adversely affect glucose tolerance. There is a lack of data from large RCTs on this issue at this point in time.

Carvedilol

Carvedilol has both alpha- and beta-blocking action. It reduces CVD mortality in HF and microalbuminuria without affecting glucose or lipid profiles. In combination with RAS blockade, more reduction in albuminuria was seen. It slows the progression of nephropathy, improves insulin sensitivity and has useful role in CAD and HF. It is underutilized as an add-on agent in hypertension with diabetes.

Nebivolol

A selective beta-blocker which improves endothelial function by increasing the nitric oxide production and reducing the oxidative stress. Study of effects of nebivolol intervention on outcomes and rehospitalization in seniors trial has shown lower incidence of new-onset diabetes.

Labetalol

Labetalol is effective in hypertensive emergencies. It is a short-acting drug and to be used for managing chronic hypertension. This is the drug of choice for pregnancy hypertension.

Role of CCBs

CCBs are ideal antihypertensive drugs. They are lipid neutral and do not disturb glucose metabolism. CCB amlodipine +/− perindopril was evaluated in comparison with atenolol and hydrochlorothiazide in a landmark study called anglo-Scandinavian cardiac outcomes trial (ASCOT).[15] Summary of all endpoints starting from primary to tertiary, including *post hoc* analysis revealed that amlodipine +/− perindopril combination is far superior compared to atenolol and hydrochlorothiazide Ref Figure 1.

Long-term mortality after BP lowering and lipid-lowering treatment in patients with hypertension in the ASCOT Legacy study: This is a 16-year follow-up results of a randomized factorial trial.

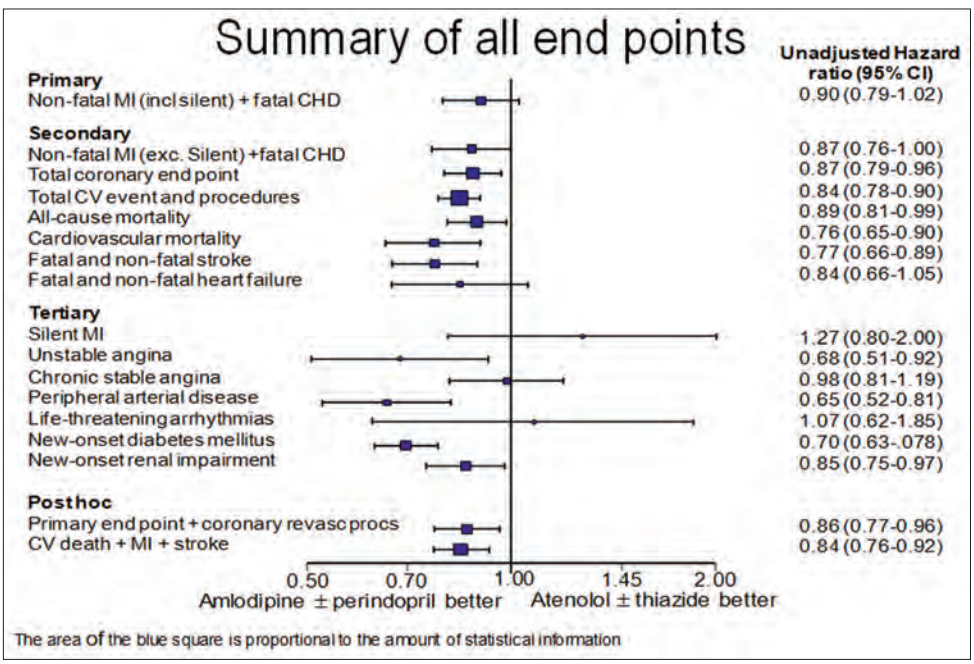

Figure 1: Anglo-scandinavian cardiac outcomes trial results

Findings show the long-term beneficial effects on mortality of antihypertensive treatment with a CCB based treatment regimen and lipid lowering with a statin. Patients on amlodipine-based treatment had fewer stroke deaths and patients on atorvastatin had fewer CV deaths (HR 0.85, 0.72–0.99, $P = 0.0395$) >10 years after trial closure. Overall, the ASCOT legacy study supports the notion that interventions for BP and cholesterol are associated with long-term benefits on CV outcomes.[16]

Avoiding CV Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study[17]

This study evaluated the efficacy of amlodipine with benazepril compared to a combination of hydrochlorothiazide with benazepril. This study had nearly 60% of participants with diabetes and a follow-up period of nearly 5 years. It was interesting to see the beneficial effects of amlodipine with benazepril to the extent of reducing relative risk of CVD by 19.6% compared to the other group. Hence, a combination of CCB with ACEI is considered superior when compared to ACEI with hydrochlorothiazide. The primary endpoint with the percentage of relative risk reduction is depicted in this [Figure 2].

Hypertension and Left Ventricular Hypertrophy (LVH)[18]

LVH is a major risk factor for CV morbidity and mortality. The study by Klingbeil *et al*. revealed that ARBs are superior for reducing LVH and LV mass compared to that of the other drugs. The efficacy rating for reducing LVH is ARB > CCB > ACEI > Diuretic > Beta Blocker in that order.

Aldosterone Blockers

Aldosterone is now known to affect insulin resistance and pancreatic beta-cell function. Spironolactone which was evaluated in randomized aldactone evaluation study in people with HF showed beneficial effects in reducing CV morbidity and mortality. Eplerenone which is a newer aldosterone blocker was evaluated in the Eplerenone Post-Acute MI HF Efficacy and Survival study. Eplerenone is considered superior when compared to spironolactone which has other side effects, including gynecomastia. 2000 participants who were diabetics in this study had shown remarkable advantages of this drug with its antihypertensive effect equivalent to ACEIs and CCBs and provided additional effect when added to ACEI and ARB. The drug reduced proteinuria in diabetic patients with nephropathy and proved to improve diastolic function. Surprisingly this drug worked well in blacks and elderly. If aldosterone blockers are added to control hypertension, a major side effect of hyperkalemia has to be monitored. These drugs are really promising for the treatment of resistant hypertension. People with diabetes should be given the benefit of this drug for proper control of BP to the goal.

Low-dose spironolactone (Normal dosage 12.5–100 mg daily) is widely recommended as a highly effective add-on drug for difficult cases of hypertension. This recommendation is based on small single-site series and *post hoc* analysis of ASCOT, which used spironolactone (12.5–25 mg daily) as a fourth-line therapy. Hyperkalemia must be avoided when using these agents in patients

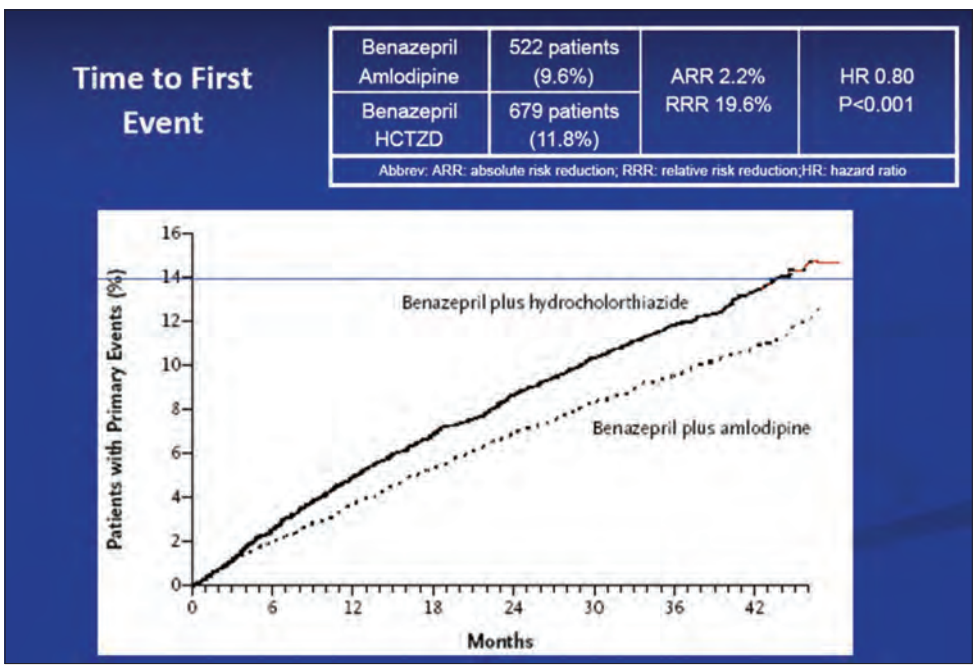

Figure 2: Avoiding cardiovascular events through combination therapy in patients living with systolic hypertension study results: Primary endpoint

with kidney disease. Aldosterone antagonist should find a place as a fourth drug in the management of resistant hypertension.

Need for Combination Therapy

Monotherapy fails in many patients who are not reaching the goal of BP. Majority of patients in general and diabetes, in particular, require combination therapy. Many studies such as HOT, ALLHAT, IDNT, and UKPDS used combination therapy with 3–4 drugs to reach the goals of BP. Combination therapy with different groups of drugs has synergistic action. Most of the patients though started with one or two drugs ultimately require 3–4 drugs for reaching the goal. Combining drugs with half the standard dose either with two or three drugs have shown beneficial effects. Fixed-dose combination in a single pill is useful for the elderly and for patients who are less compliant. American Diabetes Association (ADA), Standards of Medical Care 2019 recommendations are to administer one or more antihypertensive medications at bedtime when multiple drugs are given to control BP and the statement is reemphasized by ADA in 2019.

Priority of Antihypertensive Drug Combinations

1. ACEI plus diuretic
2. ACEI plus CCB
3. ARB plus diuretic
4. ARB plus CCB
5. Diuretic plus CCB.

Why is a CCB Preferred to a Diuretic?

CCBs are very popular antihypertensive drugs. They are generally well-tolerated, do not require monitoring with blood tests, and have proved safe and effective in many large RCTs. CCBs also have anti-anginal and some antiarrhythmic effects and seem to provide more protection against stroke than other antihypertensive agents do. Among CCB, amlodipine is the most cost-effective and metabolically neutral. Amlodipine is the best at reducing BP variability which is an independent predictor of clinical outcomes, especially the stroke. The combination of A + C is superior to A + D in improving the clinical outcomes (A: ACEI/ARB, C: CCB, D: Diuretic).

Combination therapy for Managing Hypertension

Simplifying Combination Therapy and the Optimal Drug Combination are depicted in Figures 3 and 4.

Hypertension in People with Diabetes

Hypertension is seen in 70–80% of patients with Type 2 diabetes mellitus (T2DM) and in >25% in those with Type 1 DM (T1DM). The prevalence increases with age, type of diabetes, obesity, and ethnicity. In T1DM, hypertension is mostly due to nephropathy and in T2DM, hypertension is often present at the time diabetes is diagnosed. Diabetes and hypertension are typical components of metabolic syndrome. Hypertension increases both micro and macrovascular complications of diabetes. More than 75% of diabetics die due to CVD.

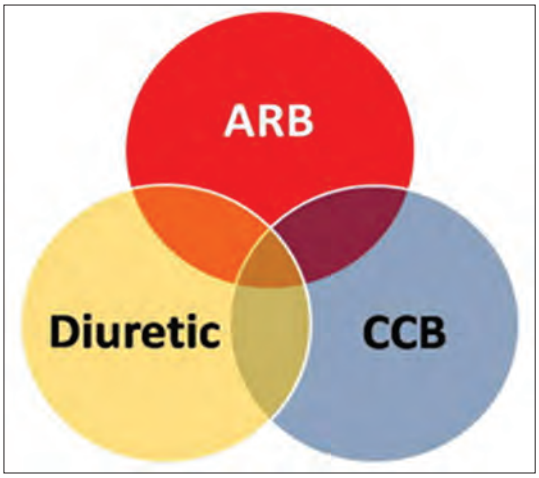

Figure 3: Simplifying combination therapy

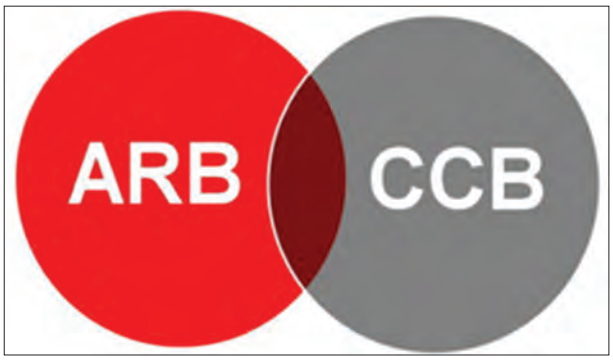

Figure 4: Optimal combination therapy for hypertension

Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) Trial[19]

Trial recruited 11,140 patients with T2DM. They were randomized to perindopril/indapamide combination or placebo and followed for a mean of 4.3 years. Those in the treatment wing had a mean reduction of systolic BP of 5.6 mmHg and diastolic BP of 2.2 mmHg. The HR for vascular events was 0.91 (95% Confidence interval [CI]: 0.83–1.00, P = 0.004). Similar reductions were noted for micro and macrovascular events. The relative risk for CV death fell by 18%.

Action to Control CV Risk in Diabetes (ACCORD) Trial[20]

Researchers randomly assigned 4,733 participants with elevated BP to a target systolic BP of either <120 mmHg (the intensive

group) or to <140 mmHg (the standard group). A variety of FDA-approved BP medications were used to reach BP goals. After an average follow-up of about 5 years, researchers found no significant differences between the intensive group and the standard group in rates of a combined endpoint, including nonfatal heart attack, nonfatal stroke, or CV death. Lowering the BP to below the standard level significantly cut the risk of stroke by about 40%. ACCORD study results show that there is no significant difference in outcome parameters for spontaneous bacterial peritonitis (SBP) levels of 119 or 130 mm Hg though there was trend toward benefits in the intensive BP lowering arm for stroke events. Serious adverse events such as syncope and hyperkalemia were more in the intensive control group.

ACCORD study may have lacked the power to establish such a difference because of the very low number of CV events that occurred in the diabetic study patients, most of whom received treatment with statins and other CV risk reduction measures. Moreover, reliance on clinic BP presents particular problems in trials of diabetic patients because of the prevelance of masked hypertension. This issue was not addressed in this trial. Two meta-analyses also concluded that in patients with diabetes protection from stroke but not myocardial infarction increases with the magnitude of reduction in BP.[21,22]

Hypertension in Patients with Diabetic Nephropathy

In RCTs, the addition of an ARB to background antihypertensive therapy was found to slow progression of nephropathy in patients with T2DM, whereas amlodipine did not.[23,24] T2DM with nephropathy is an indication for ARB therapy. There is evidence to recommend an office BP goal of 140/90 mm Hg or lower. The 2013 kidney disease improving global outcomes (KDIGO) guidelines[25] recommend a stretch goal of <130/80 mm Hg in those with significant proteinuria (urine-to-plasma albumin-to-creatinine ratio of ≥30 mg/g, a figure corresponding to ≥30 mg of urinary albumin excretion in 24 h), which is the case in most patients.

Hypertension in Patients with Nondiabetic CKD

The 2013 KDIGO guideline recommends a goal office BP of lower than 140/90 mm Hg for patients with nondiabetic nonproteinuric CKD and a stretch goal of <130/80 mm Hg with an ACEI- or ARB-based regimen for those with proteinuria.

BP Goal

Since mid-1990s most guidelines recommended 140/90 mm Hg as the threshold for diagnosing hypertension and achieving BP below this threshold should be an appropriate target of treatment. The first influential study was SHEP in which patients age 60 or older with SBP >160 mm Hg were recruited and the trial finished with the mean SBP of 143 mm Hg. Chlorthalidone was compared with placebo which proved its efficacy and safety in elderly individuals with 36% reduction in stroke and 27% reduction in CHD and 55% reduction in HF.[26] SHEP – long-term-follow up[7] with an aim to determine whether the effect of BP lowering during SHEP is associated with long-term [22 years] outcomes [CV and all cause mortality] and extended life expectancy.

Results

People on active therapy lived an average 516 days longer 205 days free of all-cause mortality not necessarily CV mortality. ACCOMPLISH study investigators looked at the event rates according to the SBP reduction. It was clearly seen that less number of events occurred when SBP was brought down between the ranges of 130 and 120 mm Hg. Events increased when SBP came down below 120–110 mm Hg. The same study also had shown maximum reduction in CV death for the same ranges of SBP reduction described above and CV death rates were higher when SBP was brought down below 120–110 mm Hg.[27]

Systolic Blood Pressure Intervention Trial (SPRINT)[28]

Current guidelines recommend SBP targets of <140 mm Hg in patients with hypertension and high CV risk. SPRINT was sponsored by the National Institutes of Health. Participants were at least 50 years of age with SBP of 130–180 mm Hg without diabetes and an increased risk of CV events. 9361 participants were assigned to an SBP target of either <140 mm Hg (the standard-treatment group) or <120 mm Hg (Intensive treatment group). Chlorthalidone was encouraged as the primary thiazide-type diuretic and amlodipine as the preferred calcium-channel blocker for this study. Primary composite outcomes: MI, ACS not resulting in MI, stroke, acute decompensated HF, or death from CV causes. Secondary outcomes: Individual components of the primary composite outcome, death from any cause, and the composite of the primary outcome or death from any cause.

SPRINT showed that among adults with hypertension but without diabetes, lowering SBP to a target goal of <120 mm Hg, as compared with the standard goal of <140 mm Hg, resulted in significantly lower rates of fatal and nonfatal CV events and death from any cause. Intensive treatment arm had a 25% lower relative risk of the primary outcome; in addition, the intensive-treatment group had lower rates of several other important outcomes, including HF (38% lower relative risk), death from CV causes (43% lower relative risk), and death from any cause (27% lower relative risk). Serious side effects such as hypotension, electrolyte abnormality, and acute kidney injury were noticed in few patients which were reversed. The trial was stopped early due to benefit after a median follow-up of 3.26 years. This study is an important landmark study which will pave the way for the guideline developers to recommend a lower SBP goal in people with hypertension and high CV risk in future guidelines.

BP Lowering for Prevention of CVD and Death[29]

A systematic review and meta-analysis which involved 123 studies with 613815 participants. The results provide strong support for lowering SBP <130 mm Hg and providing BP lowering treatment to individuals with a history of CVD, CHD, stroke, diabetes, HF, and CKD.

2017-ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high BP in adults Table 1.

Table 1: BP thresholds for and goals of pharmacological therapy in patients with hypertension according to clinical conditions

Clinical condition (s)	BP threshold, mm Hg	BP goal, mm Hg
General		
Clinical CVD or 10-year ASCVD risk ≥10%	≥130/80	<130/80
No clinical CVD and 10-year ASCVD risk <10%	≥140/90	<130/80
Older persons (≥65 years of age; noninstitutionalized, ambulatory, community-living adults)	≥130 (SBP)	<130 (SBP)
Specific comorbidities		
Diabetes mellitus	≥130/80	<130/80
CKD	≥130/80	<130/80
CKD after renal transplantation	≥130/80	<130/80
HF	≥130/80	<130/80
Stable ischemic heart disease	≥130/80	<130/80
Secondary stroke prevention	≥140/90	<130/80
Secondary stroke prevention (lacunar)	≥130/80	<130/80
Peripheral arterial disease	≥130/80	<130/80

CKD: Chronic kidney disease, HF: Heart failure, ASCVD: Atherosclerotic cardiovascular disease, BP: Blood pressure

Conclusions

Hypertension outcome trials which have been discussed above will pave the way for the clinicians to properly manage hypertension and its complications, including participants who are older and those with diabetes and CKD. Monotherapy may not be adequate in most of the patients and combination of antihypertensive drugs is needed to tackle not only complications of hypertension but also to reach the goals of BP in special situations.

References

1. Prabhakaran D, Singh K, Roth GA, Banerjee A, Pagidipati NJ, Huffman MD, *et al*. Cardiovascular diseases in India compared with the United States. J Am Coll Cardiol 2018;72:79-95.
2. Bangalore S, Kumar S, Messerli FH. Angiotensin receptor blockers and risk of myocardial infarction: Meta-analyses. BMJ 2011; 342:d2234.
3. ONTARGET Investigators, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, *et al*. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547-59.
4. Messerli FH, Bangalore S, Ruschitzka F. Angiotensin receptor blockers: Baseline therapy in hypertension? Eur Heart J 2009; 30:2427-30.
5. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, *et al*. Cardiorenal end points in a trial of aliskiren for Type 2 diabetes. N Engl J Med 2012;367:2204-13.
6. Turnbull F, Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: Results of prospectively-designed overviews of randomised trials. Lancet 2003; 362:1527-35.
7. Kostis JB, Cabrera J, Cheng JQ, Cosgrove NM, Deng Y, Pressel SL, *et al*. Association between chlorthalidone treatment of systolic hypertension and long-term survival. JAMA 2011;306:2588-93.
8. Oparil S. ALLHAT (Antihypertensive and lipid-lowering treatment to prevent heart attack trial). JAMA 2002;288:2981-97.
9. Roush GC, Holford TR, Guddati AK. Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: Systematic review and network meta-analyses. Hypertension 2012; 59:1110-7.
10. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, *et al*. Hypertension in the very elderly trial. N Engl J Med 2008;358:1887-98.
11. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, *et al* 2013 ESH/ESC guidelines for the management of arterial hypertension: The task force for the management of arterial hypertension of the European society of hypertension (ESH) and of the European society of cardiology (ESC). J Hypertens 2013; 31:1281-357.
12. O'Brien E, Parati G, Stergiou G, Asmar R, Beilin L, Bilo G, *et al*. European society of hypertension position paper on ambulatory blood pressure monitoring. J Hypertens 2013;31:1731-68.
13. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B, Guideline Development Group, *et al*. Management of hypertension: Summary of NICE guidance. BMJ 2011; 343:d4891.
14. Messerli FH, Bangalore S, Julius S. Risk/benefit assessment of beta-blockers and diuretics precludes their use for first-line therapy in hypertension. Circulation 2008;117:2706-15.
15. Dahlöf B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, *et al*. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the anglo-scandinavian cardiac outcomes trial-blood pressure lowering arm (ASCOT-BPLA): A multicentre randomised controlled trial. Lancet 2005;366:895-906.
16. Gupta A, Mackay J, Wnitehouse A, Godec T, Collier T, Pocock S. Available from: http://www.thelancet.com. [Last accessed on 2018 Aug 26].
17. Jamerson K, Weber MA, Bakris GL. ACCOMPLISH study (avoiding cardiovascular events through combination therapy in patients living with systolic hypertension) study. N Engl J Med 2008;359:23.
18. Klingbeil AU, Schneider M, Martus P, Messerli FH, Schmieder RE. A meta-analysis of the effects of treatment on left ventricular mass in essential hypertension. Am J Med 2003;115:41-6.

19. Patel A, ADVANCE Collaborative Group, MacMahon S, Chalmers J, Neal B, Woodward M, *et al*. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with Type 2 diabetes mellitus (the ADVANCE trial): A randomised controlled trial. Lancet 2007;370:829-40.
20. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, Goff DC Jr., Grimm RH Jr., *et al*. Effects of intensive blood-pressure control in Type 2 diabetes mellitus. N Engl J Med 2010;362:1575-85.
21. Bangalore S, Kumar S, Lobach I, Messerli FH. Blood pressure targets in subjects with Type 2 diabetes mellitus/impaired fasting glucose: Observations from traditional and Bayesian random-effects meta-analyses of randomized trials. Circulation 2011; 123:2799-810.
22. Reboldi G, Gentile G, Angeli F, Ambrosio G, Mancia G, Verdecchia P, *et al*. Effects of intensive blood pressure reduction on myocardial infarction and stroke in diabetes: A meta-analysis in 73,913 patients. J Hypertens 2011;29:1253-69.
23. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, *et al*. Effects of losartan on renal and cardiovascular outcomes in patients with Type 2 diabetes and nephropathy. N Engl J Med 2001;345:861-9.
24. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to Type 2 diabetes. N Engl J Med 2001;345:851-60.
25. Kidney Disease Improving Global Outcomes (KDIGO) BP Work Group. KDIGO clinical practice guideline for the management of BP in chronic kidney disease. Kidney Int Suppl 2012;2:337.
26. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the systolic hypertension in the elderly program (SHEP). SHEP cooperative research group. JAMA 1991;265:3255-64.
27. Weber MA, Bakris GL, Hester A. Systolic blood pressure and cardiovascular outcomes during treatment of hypertension. Am J Med 2013;126:501-8.
28. SPRINT Trial. Systolic blood pressure intervention trial, presented at AHA (American heart association). N Engl J Med 2015;373:2103-16.
29. Available from: http://www.thelancet.com. [Last accessed on 2015 Dec 23].

How to cite this article: Narasingan SN. Hypertension Outcome Trials: How Relevant are they in the Real World Practice of Medicine? Hypertens 2018;4(4): 192-199.

Source of support: Nil, **Conflict of interest:** None