CLINICAL INVESTIGATION

Impact of recent landmark clinical trials on hypertension treatment

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High blood pressure remains an important global cause of cardiovascular morbidity and mortality. Strategies for treating hypertension continue to change as new evidence becomes available from clinical drug trials or observational studies on hypertension treatment. As new hypertension guidelines become available, the impact of these trials become evident from changes in the recommendations of treatment, choice of drugs, options of treatment in special situations and goals of therapy. Although the results of landmark trials, conducted mainly within the last half decade, are having significant impact on the recommendations of hypertension guidelines from different societies, their results continue to stir controversies in hypertension treatment and leave many questions unanswered. However, much is expected from major hypertension guidelines to be released in the next 12 months.

Keywords: antihypertensives • blood pressure • cardiovascular • clinical drug trials • diuretics • guidelines • renin–angiotensin–aldosterone system blockade

High blood pressure (BP) is globally the most prevalent cardiovascular (CV) disease (CVD) of adults and is a major risk factor for CV and cerebrovascular morbidity and mortality [1]. Hypertension is estimated to affect as much as 1 billion people across the planet and to contribute to 7.1 million deaths per year and 92 million disability-adjusted life years [2]. The WHO reports that suboptimal BP (>115 mmHg systolic BP [SBP]) is responsible for 62% of cerebrovascular disease and 49% of ischemic heart disease, with little variation by sex [101].

It is established that the relationship between BP and CV risk is continuous such that CV risk doubles with every 20 mmHg rise in SBP or 10 mmHg rise in diastolic BP (DBP) [3]. The primary aim of hypertension treatment therefore remains the reduction of CV complications mainly through the lowering of BP.

The treatment of hypertension continues to evolve and although some recommendations for hypertension treatment from guidelines are based on consensus, most are dependent on evidence from large clinical drug trials or observational studies. However, despite the available large body of evidence for risk reduction with therapeutic intervention, the prevalence of hypertension and co-morbidities (CV, cerebrovascular and renal) remain unacceptably high.

The first guidelines for the management of hypertension were developed approximately 40 years ago and were frequently updated as new data and evidence on hypertension treatment or diagnosis and pathophysiology became available [4]. Several other hypertension guidelines, developed to meet the specific treatment objectives of groups or individual countries based on their healthcare systems have also been published and regularly updated as new evidence emerged from drug trials.

Since mid-2000, a number of important clinical trials [5–14] with large patient populations, well characterized end points and sufficient follow-up duration have been published (Table 1). The impact of evidence from these studies continue to be seen in

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the recommendations published in different guidelines for the treatment of hypertension and in the number of times they have been cited in other studies. The goals of therapy, choice and combination of drugs to be used for treatment, timing of initiation of antihypertensive drugs, benefits aside from BP control derived from the use of such drugs and the use of medications for compelling indications have often been the evidence that guidelines committees seek from clinical trials. A summary of the results of a few key clinical trials performed over the past half decade are summarized in Table 2. Seven of these trials (TRANSCEND [8], ONTARGET [9], ACCOMPLISH [10], HYVET [11], PRoFESS [12], AVOID [13] and ACCORD [14]) in 72,572 patients with hypertension and other co-morbidities were published in the last 30 months.

The aim of this review is to assess the effects of recent landmark clinical trials on hypertension treatment. In doing this, we will assess how these studies have answered the following important questions on hypertension treatment:

- Which antihypertensive agents should be used for hypertension treatment?
- Which drug combinations are preferred in treating hypertension?
- Is dual therapy with renin–angiotensin–aldosterone system (RAAS) blockade superior to single therapy?
- Choice of diuretic in hypertension treatment – thiazides or nonthiazides?
- What BP level should we be targeting?
- How should we treat hypertension in special situations?
  - Diabetes mellitus
  - Chronic kidney disease (CKD)
  - Patients with high CV risk/heart failure/coronary artery disease
  - Elderly subjects
  - Patients with isolated systolic hypertension (ISH)
  - Resistant hypertension

Based on the assessment of the impact of these trials on hypertension treatment, we will also attempt to predict the recommendations of yet to be published hypertension guidelines such as the JNC-8 and the forthcoming European Society of Hypertension guidelines.

Which agents should be used for initiation & which combinations are preferred in treating hypertension?

Recommendation for choice of first-line antihypertensive therapy has always been a source of controversy as the JNC-7 and European guidelines differ in opinion [15,16]. The JNC-7 recommendation on first-line therapy (summarized in Figure 1) was largely influenced by the ALLHAT [17] while European guidelines recommend that in the absence of compelling indications/contraindications, any from the five major classes of drugs can be used to initiate therapy [16]. In contrast the NICE guidelines, influenced by the results of the LIFE study and a meta-analysis of several trials showing reduced stroke protection with β-blockers led to removal of β-blockers from first line therapy without compelling indications [18].

In the initiation of therapy for BP control, the JNC-7 and earlier guidelines proposed the algorithm shown in Figure 1. The use of certain lifestyle modifications has been shown to be effective in lowering BP and is therefore to be recommended for all patients with hypertension. Evidence for lifestyle modifications, including reduction in weight, sodium diets and high calorie diets, have come from studies such the DASH study [19]. Although thiazide-type diuretics were recommended in the JNC-7 as the preferred initial drug for most patients with hypertension, data from more recent studies have shown the need for a more justified approach; one in which drug from any of the classes may be used to initiate therapy. This is given that drugs from several classes with similar side effect profiles can reduce CV risk to the same extent as thiazides and that the pricing advantage of diuretics over these drugs may no longer exist due to the availability of the generic formulations of these classes of drugs.

Although monotherapy, using the so-called 'step-care' approach is sometimes used for reducing BP if the desired reduction in BP is not achieved, combination therapy is the preferred initial strategy in several guidelines especially if SBP is >15 mmHg and/or DBP is >10 mmHg above goal levels [16,20,21]. In support of this, a meta-analysis of 42 trials (10,968 participants) designed to quantify the incremental effect of combining BP-lowering drugs from any two classes (thiazides, β-blockers, angiotensin-converting enzyme [ACE] inhibitors [ACE-i], and calcium-channel blockers [CCBs]) over one drug alone and to compare the effects of combining drugs with doubling dose has shown that extra BP reduction from combining drugs from two different classes is approximately five-times greater than doubling the dose of one drug [22]. Alternative two-drug combinations recommended by the ISHIB guidelines are: thiazide diuretic/aldosterone antagonist and

Table 1. Clinical trials taken into consideration in the choice of treatment recommendations by hypertension guidelines committees.

Clinical trial	Publication year	ESH 2007	NICE 2004	NICE 2006	CHEP 2005	CHEP 2010	ISHIB 2010	Ref.
VALUE	2004	+	-	+	+	-	+	[5]
ASCOT-BPLA	2005	+	N/A	+	-	-	+	[6]
ADVANCE	2007	+	N/A	N/A	N/A	-	-	[7]
TRANSCEND	2008	N/A	N/A	N/A	N/A	+	-	[8]
ONTARGET	2008	N/A	N/A	N/A	N/A	+	+	[9]
ACCOMPLISH	2008	N/A	N/A	N/A	N/A	+	+	[10]
HYVET	2008	N/A	N/A	N/A	N/A	-	-	[11]
PRoFESS	2008	N/A	N/A	N/A	N/A	+	-	[12]
AVOID	2008	NA	NA	NA	NA	-	-	[13]
ACCORD	2010	N/A	N/A	N/A	N/A	-	+	[14]

CHEP: Canadian Hypertension Education Program; ESH: European Society of Hypertension; N/A: Not available.

thiazide diuretic /β-blocker [20], although the European Society of Hypertension caution against the latter in patients with metabolic syndrome due to the increased risk of new-onset diabetes. Two-drug therapy is recommended to be given as individual monotherapies or as a single pill fixed-dose combination to simplify treatment schedule and favor compliance [16,20,21]. The ACCOMPLISH trial used combinations in both arms, comparing an ACE plus CCB with an ACE plus thiazide. Results from this trial has shown that mean BP after dose adjustment was 131.6/73.3 mmHg (benazepril/amlodipine group) and 132.5/74.4 mmHg (benazepril/hydrochlorothiazide [HCTZ] group), significantly lower ($p < 0.001$) than their respective baseline values. The ACCOMPLISH study also showed that 75.4% of patients in the benazepril/amlodipine group and 72.4% in the benazepril/CTZ group attained BP control, defined as less than 140/90 mmHg [10].

Due to various reasons such as modest incremental lowering of BP, lack of incremental lowering of pressure-related CVD and side effects of therapy (hyperkalaemia, hypotension and bradycardia), two-drug combinations that are not recommended include: ACE-i/angiotensin-receptor blockers [ARBs]; β-blocker/ACE-i; β-blocker/nondihydropyridine CCB; β-blocker/central adrenergic blocker and α-blocker/central adrenergic blocker [16,20,21].

The results of trials using combination therapy have shed much light on the selection of first line drugs for hypertension treatment. Prior to the commencement of the ACCOMPLISH and ASCOT-BPLA trials, [10,23] the most frequent combination of drugs used worldwide for the treatment of hypertension was a thiazide diuretic and a β-blocker. In the ASCOT-BPLA trial, 19,257 patients with hypertension and at least three other CV risk factors were assigned either CCB (amlodipine 5–10 mg, adding perindopril 4–8 mg as required) or β-blocker (atenolol 50–100 mg, adding bendroflumethiazide 1.25–2.5 mg and potassium as required) [23]. Fewer patients in the CCB-based regimen had a primary end point (429 vs 474; unadjusted hazard ratio [HR]: 0.90; 95% CI: 0.79–1.02; $p = 0.1052$), fatal and nonfatal stroke (327 vs 422; 0.77, 0.66–0.89, $p = 0.0003$), total CV events and procedures (1362 vs 1602; HR: 0.84; 95% CI: 0.78–0.90; $p < 0.0001$), all-cause mortality (738 vs 820; HR: 0.89; 95% CI: 0.81–0.99; $p = 0.025$) and lower incidence of developing diabetes (567 vs 799; HR: 0.70; 95% CI: 0.63–0.78; $p < 0.0001$) [23]. Results from this study contributed in shifting emphasis from β-blocker-based regimen for initiation of hypertension treatment and several guidelines have therefore referred to this trial in making recommendations for initiation of hypertension treatment (Table 1).

In the ACCOMPLISH study 11,506 patients with hypertension at high risk for CV events were assigned to receive treatment with either ACE-i (benazepril) plus CCB (amlodipine) or ACE-i (benazepril) plus diuretic (HCTZ). The primary end point was the composite of death from CV causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization.

Data from the ACCOMPLISH trial has provided the first evidence of the superiority of CCB/ACE-i combination compared with a diuretic/ACE-i combination in high risk hypertensive patients [10] and this study has clearly influenced the latest ISHIB guidelines. CCBs have been promoted alongside diuretics in the first-line treatment of hypertension if BP is <10/5 mmHg above goal and combination therapy with a RAAS inhibitor if BP >10/5 mmHg above goal. Diuretics with RAAS inhibitors are preferred only if there is evidence of volume overload. It will be interesting to see how the JNC-8

Table 2. Summary of recently published landmark clinical trials and blood pressure changes and the outcomes.

Clinical trial	No. of patients (n)	Study population	Treatment arms	Design (primary end point)	BP Δ SBP/DBP (mmHg)	Results	Ref.
VALUE	15,245	Treated or untreated hypertension and high risk of cardiac events	ARB vs CCB	RDB (composite of cardiac mortality and morbidity)	2.0/1.6	Significant and pronounced BP reduction in the CCB group; no difference in cardiac mortality and morbidity between CCB and ARB	[5]
ASCOT-BPLA	19,257	Hypertensives with other CV risk factors	BB ± THZD vs CCB ± ACE	PROBE (non-fatal MI [including silent MI] and fatal CHD)	3.0/2.0	Reduced fatal and nonfatal stroke, total CV events and procedures and all-cause mortality in the CCB group	[6]
ADVANCE	11,140	T2DM	ACE + NTHZD vs PBO	RDB (composite of major macrovascular and microvascular events)	5.6/2.2	Significant reduction in the relative risk of microvascular and macrovascular complications in the ACE + NTHZD group	[7]
TRANSCEND	5926	Patients with CVD or high-risk diabetes without heart failure	ARB vs PBO	RDB (composite outcome of CV death, MI, stroke or hospitalization for heart failure)	4.0/2.2	ARB modestly reduced the risk of the composite outcome of CV death, MI or stroke; otherwise no significant effect on primary outcome	[8]
ONTARGET	25,630	Patients with CVD or high-risk diabetes without heart failure	ACE vs ARB vs ACE + ARB	RDB (composite outcome was death from CV causes, MI, stroke or hospitalization for heart failure)	0.9/0.6; 2.4/1.4	Occurrence of the primary outcome was similar in the three groups. However, the combination group (ACE + ARB) had an increased risk of hypotensive symptoms, syncope and renal dysfunction	[9]
ACCOMPLISH	11,506	Patients with systolic hypertension	CCB + ACE vs THZD + ACE	RDB (composite of a CV event and death from CV causes)	0.9/1.1	CCB + ACE was superior to THZD + ACE in reducing CV events in high risk patients with hypertension	[10]
HYVET	3845	Elderly (≥80 years)	NTHZD/THZD + ACE vs PBO	RDB (any stroke – fatal or nonfatal)	15.0/6.1	NTHZD, with or without ACE, is associated with significant reduction in primary outcome and death	[11]

ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blocker; BB: β-blocker; BP: Blood pressure; CCB: Calcium-channel blocker; CHD: Coronary heart disease; CV: Cardiovascular; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; DRI: Direct renin inhibitor; MI: Myocardial infarction; NTHZD: Non-thiazide diuretic; PBO: Placebo; R 2x2 FD: Randomized 2x2 factorial design; RDB: Randomized, double-blind; SBP: Systolic blood pressure; T2DM: Type 2 diabetes mellitus; THZD: Thiazide diuretic.

Table 2. Summary of recently published landmark clinical trials and blood pressure changes and the outcomes (cont.).

Clinical trial	No. of patients (n)	Study population	Treatment arms	Design (primary end point)	BP Δ SBP/DBP (mmHg)	Results	Ref.
PRoFESS	20,332	Patients with recent ischaemic stroke	ARB vs PBO	RDB (recurrent stroke of any kind)	3.8/2.0	Nonsignificant reduction in subsequent stroke and CVD events in the ARB group	[12]
AVOID	599	T2DM with nephropathy	DRI + ARB vs ARB + PBO	RDB (reduction in albumin:creatinine ratio at 6 months)	2.0/1.0	Significant reduction (20%) in urine albumin:creatinine ratio in the active arm	[13]
ACCORD	4733	T2DM	Intensive vs standard	R 2x2 FD (composite of nonfatal MI, nonfatal stroke or death from CV causes)	14.2/6.1	No difference in outcomes between both groups	[14]

ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blocker; BB: β-blocker; BP: Blood pressure; CCB: Calcium-channel blocker; CHD: Coronary heart disease; CV: Cardiovascular; CVD: Cardiovascular disease; DBP: Diastolic blood pressure; DRI: Direct renin inhibitor; MI: Myocardial infarction; NTHZD: Non-thiazide diuretic; PBO: Placebo; R 2x2 FD: Randomized 2x2 factorial design; RDB: Randomized, double-blind; SBP: Systolic blood pressure; T2DM: Type 2 diabetes mellitus; THZD: Thiazide diuretic.

committee will view the results of the ACCOMPLISH and ASCOT studies given the important emphasis of the ALLHAT study in the JNC-7 recommendations. The JNC-8 recommendations on first line and combination therapy are therefore awaited with interest.

Which diuretics should be used for the treatment of hypertension?

Diuretic-based strategies for hypertension treatment have for many decades been proven to be effective for BP lowering and for the prevention of CV diseases. Most guidelines recommend a thiazide diuretic without choosing a specific agent. HCTZ is the most commonly prescribed antihypertensive used in the USA, whereas bendroflumethiazide is widely used in the UK. These were the thiazide diuretics used in the ACCOMPLISH and ASCOT studies, respectively. The ALLHAT study showed the efficacy and safety of chlorthalidone compared with lisinopril and amlodipine in hypertension especially in the prevention of heart failure, stroke and CV outcomes in African-Americans. [17]. In the SHEP study, high dose HCTZ showed significant reductions in CV end points and guidelines have also stressed the importance of a diuretic as initial therapy for ISH in older patients [24].

However, in recent years considerable controversy has developed regarding the choice of HCTZ versus chlorthalidone. Kaplan in his recent commentary suggests that two facts appear to have been overlooked [25]. First, low-dose HCTZ (12.5–25 mg) has never been shown to reduce CV morbidity or mortality although it increases the antihypertensive efficacy of whatever drug is added. Secondly chlorthalidone in doses of 12.5–25 mg has been repeatedly shown to reduce CV morbidity and mortality in randomized controlled clinical trials [26]. In a review, chlorthalidone was found to be 1.5–2-times more potent than HCTZ and provided superior 24 h ambulatory BP control [27]. However in the PHYLLIS study BP lowering was similar to an ACE-i but there was greater progression of carotid intimal media thickness [28]. The incidence of hypokalemia also seems to be similar between the two agents.

The impact of these findings may be more clearly seen when comparing the recommendations on use of diuretics for hypertension treatment in the 2003 and 2010 ISHIB guidelines [20,29]. In the later guidelines, chlorthalidone is recommended over HCTZ in most clinical situations. It is of interest to speculate if the outcomes of ACCOMPLISH and ASCOT would have changed if chlorthalidone was used in preference to HCTZ and bendroflumethiazide respectively, and to see if the JNC-8 recommendations will address this issue. We anticipate a shift towards chlorthalidone. Little attention is given to indapamide, a nonthiazide

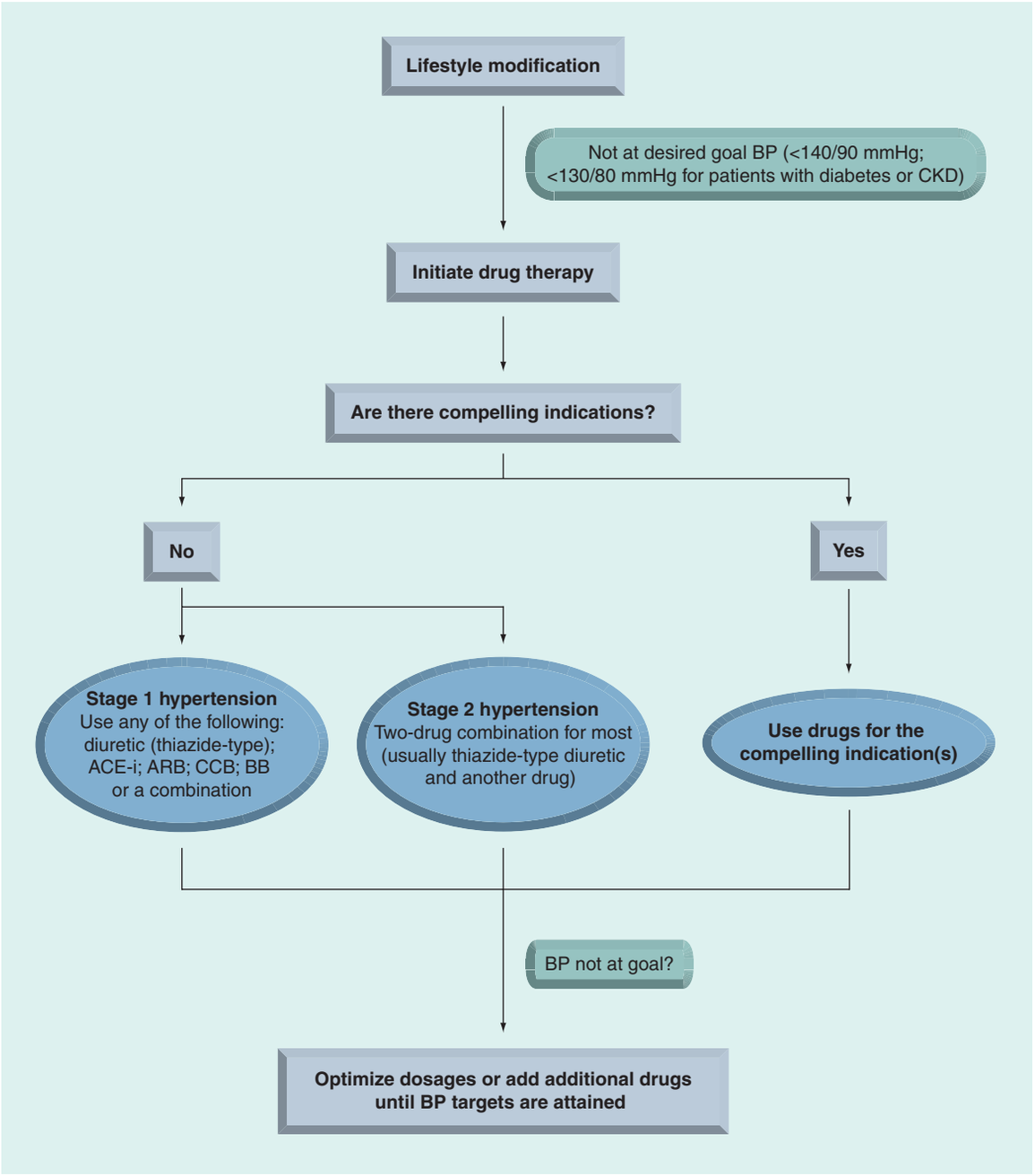

Figure 1. Algorithm for the treatment of hypertension.
ACE-I : Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker; BB: β blocker; BP: Blood pressure; CCB: Calcium-channel blocker; CKD: Chronic kidney disease.

diuretic, in the USA-orientated literature as it is not available in this country. It appears to have a slightly better metabolic profile than HCTZ.

A meta-analysis of 44 studies comparing the blood lipid and BP responses during hypertension treatment with indapamide and thiazides showed that total cholesterol increased from baseline by 1.4% on indapamide, 3.8% on low-dose thiazides, and 6.3% on high-dose thiazides, the change from baseline was significantly greater for high-dose thiazides than for indapamide ($p < 0.01$) [30]. Studies using nonthiazide diuretics have not shown significant differences in the occurrence of these metabolic adverse events between the diuretic and nondiuretic treated arms [7,11,31]. However of greater

importance is that low dose indapamide has been shown to have clinical efficacy in randomized controlled trials. In the PROGRESS the use of indapamide together with perindopril was associated with significant stroke reduction [31].

In the ADVANCE study designed to assess the effects of routine administration of perindopril and indapamide combination compared with a placebo on serious vascular events in patients with diabetes; total cholesterol, high-density lipoprotein cholesterol, fasting plasma glucose and HbA1c levels were reported not to be different between the randomized groups [7]. However, there was a significant reduction in the relative risk (RR) of microvascular and macrovascular complications in the group treated with a nonthiazide diuretic. Other guidelines still recommend thiazide diuretics for the treatment of hypertension [16,21].

Are ACE-i & ARB equal & is dual therapy with RAAS blockade superior to single therapy?

The clinical benefits (reduction in rates of death, myocardial infarction, stroke, heart failure in patients with known coronary artery disease or left ventricular dysfunction and proteinuria) of RAAS blockade with an ACE-i has been shown from various studies. ARBs had showed significant reductions in end points in studies mainly addressing renal outcomes and stroke outcomes, but there were concerns that ARBs were inferior in regard to reductions of myocardial infarctions. It was also suggested that greater inhibition of the RAAS by combining ACE-i and ARBs may achieve greater efficacy in lowering CVS end points. The ONTARGET program addressed these issues by comparing rampril with telmisartan, and telmisartan and ramipril in combination in high-risk patients with CV disease or diabetes mellitus but without heart failure [9]. Telmisartan was found to be non-inferior to ACE-i (ramipril) but with the added benefit of not causing cough or angioedema. Compared with ramipril, the dual-therapy group there was no difference in the primary composite end point, but there were more serious adverse event. Hypotensive symptoms (4.8 vs 1.7%; $p < 0.001$), syncope (0.3 vs 0.2%; $p = 0.03$), and renal dysfunction (13.5 vs 10.2%; $p < 0.001$) occurred more frequently in the combination group [9].

A meta-analysis of four studies (VALIANT Trial [32], CHARM-Added Trial [33], ValHeft [34] and RESOLVD Trial [35]) has compared dual therapy of ACE-i and ARBs with monotherapy (ACE-i or placebo) and assessed for medication discontinuations due to adverse effects, worsening renal function (increase in serum creatinine >0.5 mg/dl and up to a doubling over baseline values), hyperkalaemia (serum potassium level >5.5 mEq/l), and symptomatic hypotension in those studies. Adverse events was reported to be significantly increased with dual therapy versus control treatment in patients with chronic heart failure (3.3 vs 1.5%; RR: 2.17; 95% CI: 1.59–2.97) [36]. Also, there was a significant increase in the risk of hyperkalaemia (3.5 vs 0.7%; RR: 4.87; 95% CI: 2.39–9.94) and significant increase in the risk of worsening renal function in acute myocardial infarction with symptomatic LV dysfunction (4.8 vs 3.0%; RR: 1.61; 95% CI: 1.31–1.98) [36].

Thus, the combination of an ACE-i and ARB has only been shown to be associated with increased adverse events without an increase in benefit. Recent guidelines have therefore not recommended the use of combination of ACE-i and ARB [20,21]. The recently published AVOID trial in which dual therapy with a direct renin inhibitor (DRI) and an ARB was compared with combination of placebo and ARB did not show significant difference in adverse events between both groups [13]. The ongoing ALTITUDE, a much larger study of patients with diabetic nephropathy, comparing treatment with a DRI and ACE-i/ARB with placebo and ACE-i/ARB is expected to shed more light on dual therapy with RAAS blockade [37]. If like the AVOID trial, the ALTITUDE trial shows benefit in the active arm with no significant difference in side effects between the two arms, combination therapy of an ACE-i/ARB with a DRI may become the recommended choice of dual therapy for reno-protection by future guidelines. The VA-NEPHRON-D study is equally expected to add to the strength of evidence for dual therapy with RAAS blockade [38].

What BP level should we be targeting?

The result of recent studies has led to a major reappraisal of lower BP targets particularly in patients at higher CV risk. The HOT and the ABCD studies provided evidence for lower BP targets in diabetes mellitus [39,40]. In the HOT study, there was a 51% reduction in major CV events in the group with DBP ≤80 mmHg compared with the group with DBP ≤90 mmHg (p for trend = 0.005) [39]. Similar results were obtained in the ABCD study in which fewer deaths occurred after a mean of 5.3 years of follow up in patients randomized to the intensive BP group (10 mmHg below baseline DBP) than in patients in the moderate BP control group (DBP: 80–89 mmHg; 5.5 vs 10.7%; $p = 0.037$) [40]. Hence, most guidelines recommend BP treatment in diabetes to target levels of ≤130/80 mmHg, although there was no convincing evidence in controlled clinical trials that lowering BP ≤140 mmHg in diabetics resulted in improved outcomes.

The recently published ACCORD and ADVANCE studies have shed further light on this issue. The ADVANCE study (see below) the SBP in

the perindorpil/indapamide arm was 140.3 mmHg compared with 134.7 mmHg in standard therapy arm resulted in a small but significant reduction in combined micro and macrovascular complications and mortality providing the first evidence for lower targets for SBP in diabetics.

In contrast the ACCORD study investigated whether intense lowering of SBP in diabetes to normal levels (SBP <120 mmHg) reduces major CV [14]. The study compared two levels of BP control: intensive therapy (SBP <120 mmHg) or standard therapy (SBP <140 mmHg) in 4733 participants with Type 2 diabetes mellitus (T2DM). After 1 year, the mean SBP was 119.3 mmHg in the intensive therapy group and 133.5 mmHg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group ($p = 0.20$) while the annual rates of death from any cause were 1.28 and 1.19% in the two groups, respectively ($p = 0.55$). The annual rate of stroke was higher in the standard therapy group (0.32 vs 0.53%; $p = 0.01$). Serious adverse events attributed to antihypertensive treatment occurred in 3.3% in the intensive-therapy group in 1.3% in the standard-therapy group ($p < 0.001$) [14]. From epidemiological studies the difference in BP between the intensive and standard treatment group should have resulted in substantial reductions in CV events. Although there was no overt harm and some benefit on stroke reduction it is possible that some guidelines may revise the target for diabetics to 140/90 mmHg.

In high risk patients, clinical trials and systematic reviews have failed to show evidence for lower BP targets in this population. In the PROVE IT-TIMI 22 trial (pravastatin 40 mg versus atorvastatin 80 mg in acute coronary syndrome patients) [41], a J- or U-shaped curve association was observed to exist between BP and the risk of future CV events. The lowest event rates occurred in SBP of 130–140 mmHg and DBP of 80–90 mmHg and a relatively flat curve for SBP: 110–130 mmHg and DBP: 70–90 mmHg was observed, suggesting that BP <110/70 mmHg may be harmful to such patients in keeping with the JNC-7 guidelines [15,41]. The ongoing SPRINT [102] will examine the effect of a SBP target of 120 versus 140 mmHg in high risk patients with CVS disease and will shed further light in this issue. Similarly, in patients with CKD a recent systematic review of three large CKD trials for lower BP targets in CKD patients, although showing benefit for patients with proteinuria, failed to conclusively show benefit for CV disease reduction [42]. Also, the ongoing HALT-PKD trial may provide additional information on lower BP targets in patients with CKD (autosomal dominant polycystic kidney disease) [43]. These results rekindle the debate surrounding BP targets in hypertensives, especially in patients with diabetes mellitus. Do lower targets necessarily mean better outcomes or should current targets continue to be adhered to? The more recent guidelines [20,21] have not changed their recommendations on BP targets and it is debatable whether future guidelines will change the current recommendations on BP goals.

One factor, amongst several, that affects how BP target is interpreted and possibly attained relates to how it was measured in the first place. In clinical trials, BP readings are often taken in the clinic or office and are subject to both white coating and masking. Ambulatory BP monitoring, not only provides a more accurate assessment of overall BP status including nocturnal dipping, but is a better predictor of target organ damage and clinical outcomes [44–46]. Clinical decisions based solely on office BP may lead to overestimation and underestimation of control leading to inappropriate clinical decisions especially when BP is close to target [47].

How should hypertension be treated in special situations?

Diabetes

A summary of treatment guideline recommendations for hypertension in special situations such as diabetes mellitus, the elderly patient, ISH, CKD, patients with a high risk of CV disease and in heart failure is shown in Table 3. BP is an important determinant of the risks of macro- and micro-vascular complications of T2DM, and guidelines recommend intensive lowering of BP for diabetic patients with hypertension to targets of ≤130 mmHg (SBP) and ≤80 mmHg (DBP) preferably using an ACE-i or an ARB.

In the ADVANCE study after a mean follow-up of 4.3 years, there was a reduction in the RR of a major macrovascular or microvascular event in patients treated with ACE-i and diuretic compared with those on placebo ($p = 0.04$) [7]. Compared with patients assigned placebo, those assigned active therapy had a mean reduction in SBP of 5.6 mmHg (95% CI: 5.2–6.0; $p < 0.0001$) and DBP of 2.2 mmHg (95% CI: 2.0–2.4; $p < 0.0001$) and the RR of death from CVD was also significantly reduced in the active treatment arm ($p = 0.03$). The ADVANCE investigators concluded that routine administration of a fixed combination of ACE-i (perindopril) and diuretic (indapamide) to patients with T2DM was well tolerated and reduced the risks of major vascular events, including death [7].

Also, the ACCORD trial provided further evidence that in patients with diabetes, further lowering of BP (SBP <120 mmHg) does not add any additional benefits as more patients treated to this goal suffered more adverse events related to antihypertensives than those in the standard-therapy group (3.3 vs 1.3%; $p < 0.001$) [14].

Table 3. Preferences for anti-hypertensive drugs by co-morbidity.

Anti-hypertensive drug	Heart failure	Post-myocardial infarction	CAD/angina	Diabetes	CKD	Stroke prevention	High vascular disease risk
Diuretic	Likely benefit or safety proven		Likely benefit or safety proven		Likely benefit or safety proven	Likely benefit or safety proven	Likely benefit or safety proven
BB	Compelling indication	Compelling indication	Compelling indication		Likely benefit or safety proven		
ACE	Compelling indication	Compelling indication	Compelling indication	Compelling indication	Compelling indication	Compelling indication	Compelling indication
ARB	Compelling indication	Compelling indication	Likely benefit or safety proven	Compelling indication	Compelling indication	Compelling indication	Compelling indication
CCB	Contra-indicated[†]		Compelling indication	Likely benefit or safety proven	Likely benefit or safety proven		
AA	Compelling indication	Compelling indication			Contra-indicated		

[†]CCBs to be avoided unless needed to control BP or anginal symptoms.

AA: Aldosterone antagonist; ACE: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin-receptor blocker; BB: β-Blocker; CAD: Coronary artery disease; CCB: Calcium-channel blocker; CKD: Chronic kidney disease.

In a recent meta-analysis of randomized clinical trials of antihypertensive therapy in patients with T2DM (1965–2010), Bangalore *et al.* reported that intensive BP control was associated with a 10% reduction in all-cause mortality (odds ratio: 0.90; 95% CI: 0.83–0.98), a 17% reduction in stroke, and a 20% increase in serious adverse effects, but with similar outcomes for other macrovascular and microvascular (cardiac, renal and retinal) events compared with standard BP control [48]. Other analysis (Bayesian random effects model) provided similar results and a meta–regression analysis showed continued risk reduction for stroke to a SBP of <120 mmHg. However, at levels <130 mmHg, there was a 40% increase in serious adverse events with no benefit for other outcomes. They therefore concluded that in patients with T2DM, an SBP goal of 130–135 mmHg is acceptable as lower targets were not associated with cardiac, renal or retinal benefits, although risk of stroke was lower [48].

It is therefore clear that in diabetics the often touted concept of the 'lower the better' is no longer tenable and it is likely that future guidelines are not expected to change current recommendations for BP targets (≤130/80 mmHg) in patients with diabetes, although there may be consideration for a target <140/90 mmHg.

■ Elderly patients & ISH

Most guidelines recommend a cautious approach to treating hypertension in elderly patients since they are frail, are prone to a substantial fall in BP during treatment and are more likely to have white coat or pseudohypertension [16,20,21]. Nevertheless, these guidelines recommend antihypertensive drug treatment in older patients as they show benefit in terms of reduced CV morbidity and mortality, irrespective of whether they have systolic and diastolic hypertension or ISH. Generally, the guidelines have recommended for drug treatment in the elderly to be initiated with any class of antihypertensive agent and for the BP goal to be the same as in younger patients (≤140/ 90 mmHg) if tolerated.

In a number of recent clinical trials, the mean age of patients has been reported to be >60 years [8,14]. Of the 11,506 participants in the ACCOMPLISH trial, over 40% were reported as being ≥70 years of age while the HYVET trial specifically randomized patients ≥80 years of age [10,11]. In the HYVET trial with the primary end point of fatal or nonfatal stroke, patients with sustained elevation of SBP (≥160 mmHg) were randomized to receive a diuretic (indapamide) or matching placebo with the option of the ACE-i (perindopril), or matching placebo added if necessary in order to achieve the target BP of 150/80 mmHg [11]. At 2 years, the mean sitting BP was 15.0/6.1 mmHg lower in the active-treatment group than in the placebo group with the target BP reached in 48.0 and 19.9% of patients, respectively ($p < 0.001$). Importantly, active treatment was associated with a 30% reduction of stroke (95% CI: -1–51; $p = 0.06$), a 39% reduction of death from stroke

(95% CI: 1–62; p = 0.05), a 21% reduction in all cause mortality (95% CI: 4–35; p = 0.02), a 23% reduction in CV death (95% CI: –1–40; p = 0.06), and a 64% reduction of heart failure (95% CI: 42–78; p < 0.001). Also, fewer serious adverse events were reported in the active-treatment group (358 vs 448 in the placebo group; p = 0.001) [11]. Despite participants being treated to a target of ≤150/80 mmHg in the HYVET trial, guidelines have not adopted this as the goal of treatment in elderly patients. It is unlikely that future guidelines will change this target. Similar benefits in the end points had been demonstrated in elderly patients with hypertension who were treated with a diuretic in the SHEP study [49].

In the ACCOMPLISH study which also targeted elderly patients either treated with ACE-i and CCB or diuretic and ACE-i, an absolute risk reduction of 2.2% and a RR reduction of 19.6% (HR: 0.80; 95%CI: 0.72–0.90; p < 0.001) was reported in the ACE-i and CCB group suggesting that this combination is superior to use of diuretic and ACE-i for treating hypertension in elderly patients [10].

The second ANBP-2, designed to compare the outcomes in elderly subjects (65–84 years) with hypertension treated with ACE-i or diuretics reported similar BP reductions in both groups but lower CV events or all cause mortality in the ACE-i treated group (p = 0.05). Male subjects had significantly lower reductions in the end points (p = 0.02) compared with females (p = 0.98) in the ACE-i treated groups [50].

No matter how the results of these studies are interpreted, it is clear that there is significant benefit in treating hypertension in elderly patients. However, since ISH is very common in the elderly, the use of ACE-i and CCB may show superiority in BP control and reduction of CV diseases than other agents. The choice of drug(s) to be used in the elderly for BP control may follow the general recommendations provided in the guidelines. Hence, being elderly may not necessarily constitute a special situation for hypertension treatment as much as the underlying co-morbidity present in the elderly hypertensive patient.

■ Patients with high CVD risk

The VALUE trial tested the hypothesis that for the same BP control, ARB (valsartan) would reduce cardiac morbidity and mortality more than CCB (amlodipine) in hypertensive patients at high CV risk [5]. After a mean of 4.2 years of follow up, BP was reported to be more pronouncedly reduced in the CCB group, especially in the early period of the study (BP 4.0/2.1 mmHg lower in CCB than ARB group after 1 month; 1.5/1.3 mmHg after 1 year; p < 0.001 between groups). However, the primary composite end point was not significantly different between both groups (p = 0.49) [5].

The TRANSCEND and PRoFESS studies [8,12] have assessed the effects of BP treatment in high risk hypertensives. In the PRoFESS study, 20,332 patients with recent ischaemic stroke were randomly assigned to receive ARB (telmisartan) or placebo but the study could not demonstrate significant reduction in the primary end point (recurrent stroke; p = 0.23) or secondary end points (major CV events; p > 0.05) in patients treated with ARB. Mean BP was 3.8/2.0 mmHg lower in the ARB group than the placebo group [12]. Similarly, in the TRANSCEND study; which was the ACE-i intolerant arm of the ONTARGET Study, the ARB (telmisartan) had no significant effect on the primary outcome of the study even though it modestly reduced the risk of the composite outcome of CV death, myocardial infarction, or stroke [8]. The lack of benefit of telmisartan seen in these trials may reflect that these studies are underpowered to detect differences where overall CVS risk prevention is optimized or perhaps the diminishing effects of lower BP targets.

■ Chronic kidney disease

There are not many landmark trials published within the last decade assessing hypertension treatment with hard renal end points. The AVOID trial compared dual therapy of a DRI (aliskiren) and an ARB with placebo and ARB. At the end of the study, the mean BP in the DRI group was 2/1 mmHg lower than that in the placebo group (p = 0.07 for SBP; p = 0.08 for DBP) [13]. Daily treatment with DRI, as compared with placebo, reduced the mean urinary albumin:creatinine ratio by 20% (95% CI: 9–30; p < 0.001), with a reduction of 50% or more in 24.7% of the patients who received DRI as compared with 12.5% of those who received placebo (p < 0.001). All adverse events occurred at similar frequencies between the DRI group and the placebo group (66.8 vs 67.1%). Hyperkalaemia with serum potassium ≥6.0 mmol/l occurred in 4.7% of the DRI group compared with 1.7% in the placebo group (p = 0.06) [13].

Although the AVOID trial shows that dual therapy with DRI and ARB may have renoprotective effects independent of BP lowering in patients with hypertension,T2DM, and nephropathy, two limitations of the trial are the relatively small sample size (599 patients) and the short follow up period (24 weeks) [13]. The much larger ALTITUDE trial with longer follow up period is expected to provide broader answers regarding these end points and adverse events profile [36].

In the African–American study of kidney disease (AASK) study, ACE-i (ramipril) use was associated with significant reduction of composite outcome compared with β-blocker (22%; 95% CI: 1–38; p = 0.04) and CCB (38%; 95% CI: 14–56; p = 0.004) in

African-American patients with hypertensive renal disease [51]. The IDNT and RENAAL study also showed reduction in end points associated with use of ARB [52,53]. Guidelines for treatment of hypertension have therefore recommended use of an agent that blocks the RAAS in patients with CKD (elevated serum creatinine and/or proteinuria or microalbuminuria).

Resistant hypertension

Resistant arterial hypertension, the inability to control BP despite treatment with at least three drugs (including a diuretic) in adequate doses and after exclusion of spurious hypertension, is estimated to affect 25–30% of hypertensive patients [16,54]. BP control remains substantially low worldwide despite the availability of drugs for hypertension treatment [55]. Although a number of small studies have evaluated possible drug treatments in patients with resistant hypertension, only in one study, the Symplicity HTN-2 trial, have patients been randomized to have renal sympathetic denervation performed for treatment of resistant hypertension [56].

Using the Symplicity catheter as a means to ablate the renal sympathetic nerves, 106 patients were randomly allocated to renal denervation group or control group (maintenance of previous treatment alone) [56]. Office-based BP measurements in the renal denervation group significantly reduced by 32/12 mmHg from baseline values ($p < 0.0001$) but did not differ from baseline values in the control group ($p = 0.77$ for SBP and $p = 0.83$ for DBP). Between-group differences in BP at 6 months were 33/11 mmHg ($p < 0.0001$) and 84% of patients who underwent renal denervation had a reduction in SBP of 10 mmHg or more, compared with 35% of controls ($p < 0.0001$) [56].

The guidelines for hypertension treatment continue to recommend, based on consensus rather than evidence, for patients with resistant hypertension to be treated with addition of aldosterone antagonists (eplerenone, spironolactone) [16,20,21]. In an analysis conducted to determine the effect of spironolactone on BP among 1411 participants in the ASCOT-BPLA study, spironolactone therapy was associated with reduction of mean BP by 21.9/9.5 mmHg (95% CI: 20.8–23.0/9.0–10.1 mmHg; $p < 0.001$) after a median duration of use of 1.3 years [57]. Frequently reported adverse events included gynaecomastia or breast discomfort and biochemical abnormalities (principally hyperkalaemia), recorded in 6% and 2% of participants, respectively. Other studies have reported similar results [58]. However, the Symplicity HTN-2 trial provides solid evidence for treatment of this group of patients using alternative approaches. It remains to be seen if guidelines will adopt this approach for the treatment of hypertension.

Future perspective

The recent landmark clinical trials have provided with important new information on the treatment of hypertension although they have left us with new uncertainties. It is now clear that CCBs are firmly entrenched in first line therapy for most hypertensives, and the role of β-blockers outside compelling indications is less certain. There may be greater movement to recommend the use of nonthiazide diuretics such as chlorthalidone and indapamide, but given the widespread availability of HCTZ in fixed drug combinations this is unlikely to occur. BP targets will continue to provoke controversy and whether the epidemiological evidence for lower targets in high risk patients will outweigh the lack of definitive evidence from controlled clinical trials. However there is a clear movement away from very low targets that were previously touted in high risk patients. Aldosterone antagonists are gaining acceptance for the use in resistant hypertension but prospective controlled trial data is lacking. It also remains to be seen whether nonpharmacological interventions like renal symphathectomy will be extended to less severe hypertensives to reduce or eliminate antihypertensive therapy. Despite extensive research into the genetic causes of essential hypertension it is anticipated that a pharmacogenetic approach to hypertension is not realizable in the foreseeable future.

Executive summary

- Combination therapy with angiotensin-converting enzyme inhibitors and calcium-channel blockers is effective and preferred for initiating treatment of hypertension.
- Dual therapy with a renin–angiotensin–aldosterone system blockade is not recommended for treatment, however results from ongoing studies are expected to shed more light on this subject.
- Nonthiazide type diuretics which are unassociated with the adverse metabolic profiles seen with thiazides and are effective for blood pressure reduction are the preferred choice of diuretics.
- There is still no evidence that 'lower is better' in targeting blood pressure goals. And although current goals are still recommended, the controversies surrounding a more intensive treatment of hypertension will continue.
- Current recommendations for hypertension treatment in special situations such as diabetes, chronic kidney disease, the elderly and patients with high cardiovascular risk remain valid and should be followed until new evidence become available.
- Aldosterone antagonists should be used to treat resistant hypertension, however, renal sympathetic denervation may soon become recommended in guidelines for such treatment.

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