Chapter

93 Evolving Clinical Strategy in the Treatment of Hypertension

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EVOLVING CLINICAL STRATEGY IN THE TREATMENT OF HYPERTENSION

Hypertension is the most important preventable cause of cardiovascular disease in developed countries[1]. The benefits of lowering blood pressure are no longer disputed and are supported by the most impressive evidence base in clinical medicine. Yet, it remains both under diagnosed and under treated (Fig. 1)[2]. To circumvent these problems, scientific bodies have been issuing guidelines periodically. One of the popular guidelines followed world over is the JNC VII guidelines released in 2003 (Fig. 2)[3]. Newer data have become available since then, making us take a fresh look at the old problem. Are there drug-specific benefits that go beyond the powerful independent benefits of blood pressure lowering? Are clinical trials, which focus on higher risk patients and "hard clinical end points," the best way to assess the potential benefits of drug treatments that are likely to be applied for half of a patient's lifetime? Are we endeavoring to prevent events or prevent the evolution of a destructive disease process? In this regard, what is the role of surrogate or intermediate end points? Is it appropriate to have an arbitrary threshold to define "hypertension," or should we instead consider the benefits of "blood pressure-lowering" in the context of a patient's overall cardiovascular disease (CVD) risk?

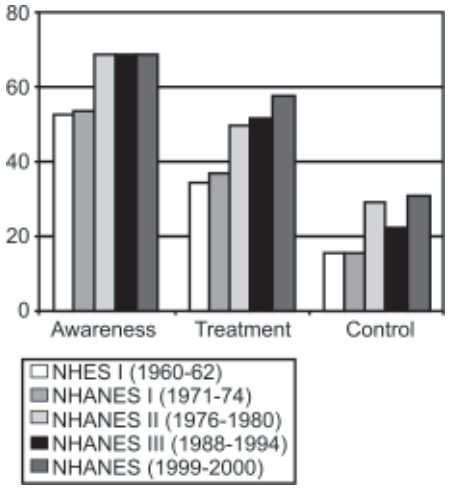


Fig. 1: Epidemiology of uncontrolled hypertension in the United States[2]

These are key questions for which a proper answer is still elusive. Complex pathophysiological processes underlying hypertension makes the management complex as well. Meta-analysis of betablockers and publication of ASCOT-BPLA study have cast doubts over the JNC VII guidelines. The apparent shortfall in the prevention of CVD in early hypertension trials than expected from observational data may be due to the drugs – beta-blockers and diuretics. The early antihypertensive trials employed older drugs like betablockers compared to placebo. Only in the past decade active comparative trials were conducted. How effective are various drug classes in preventing CAD, stroke, heart or renal failure and new onset diabetes?

JNC VII guidelines (Fig. 2)[3] introduced a new category called Prehypertension (systolic BP 120-139 and diasolic BP of 80-89 mmHg) for which lifestyle modification is advocated and recommended diuretics for most (based on ALLHAT study) for initial therapy of hypertension without compelling indication. Stages II and III were clubbed together (risk is same in both stages). Certain high risk conditions are compelling indications

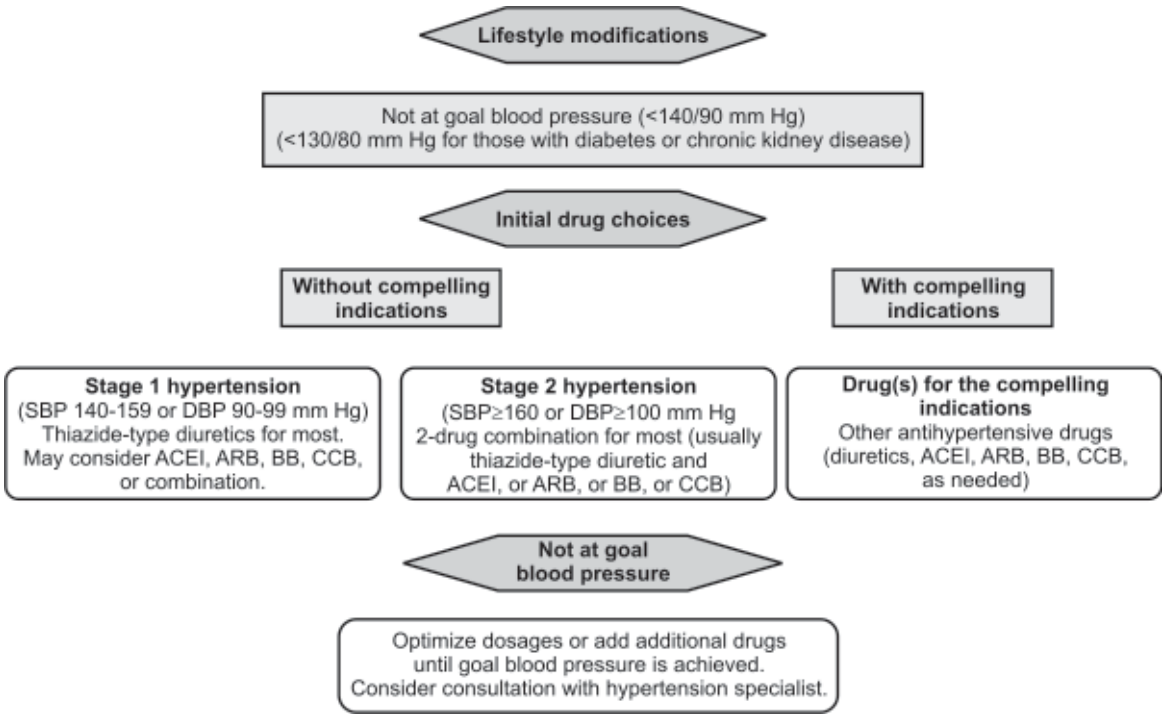


Fig. 2: Algorithm for treatment of hypertension. A = ACE inhibitor (or ARB if ACEi-intolerant); C = calcium channel blocker; D = thiazide-type diuretic. Beta-blockers are not a preferred initial therapy for hypertension but are an alternative to A in patients <55 years in whom A is not tolerated, or contraindicated (includes women of child-bearing potential). Black patients are only those of African or Caribbean descent. In the absence of evidence, all other patients should be treated according to the algorithm as non-black

for use of other classes of drugs (pre-existing CAD, heart failure, Diabetes etc). Most patients will require two or more drugs and if BP is > 20/10 mm Hg above goal, one of which should usually be a thiazide diuretic.

Evolution of Hypertension Studies

Early studies were placebo compared, where as, newer studies are head to head, making it larger and complex in view of stiffer targets (in essence comparison of treatment regimens rather than individual drugs). The end points have become composite in view of large sample size required. The Blood Pressure Lowering Treatment Trialists Collaborative (BPLTTC) published their most recent meta analysis in 2003[4]. It incorporated data from 29 randomized, controlled trials involving 162,341 patients, and the mean duration of follow-up ranged from 2.0 to 8.0 years, providing over 700,000 patient-years of follow-up. The overall mean age of trial participants was 65 years, and 52% were men. As expected, angiotensin-converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) were both more effective than placebo at reducing the risk of major cardiovascular events by 22% (confidence interval [CI] 17% to 27%) and 18% (CI 5% to 29%), respectively (Fig. 3). When the main drug classes were compared "head-to head," (i.e., conventional therapy [thiazide and/or betablocker], ACE inhibitors, or CCBs), there were no significant differences in major cardiovascular outcomes or cardiovascular mortality (Fig. 4)[8].

ASCOT-BPLA study is the first randomized-controlled study to show superiority of amlodepine-perindopril (new drugs) combination over atenolol-bendro-flumethiazide (old drugs) on major cardiovascular events and new onset diabetes (Fig 5)[5]. The large study, involving 19257 patients was stopped prematurely after 5.5 years by ethical committee. The average age in the study was 63 years and there was greater and earlier fall in BP with newer drugs. The better results with newer drugs may be due to a more aggressive approach to vascular intervention, greater fall in mean BP, more effect on central aortic pressure, non BP lowering effects of newer drugs, adverse interactions between atenolol and diuretic or higher baseline BMI, serum triglycerides, creatinine concentrations, and fasting blood glucose levels and lower HDL values in atenolol group. CAFÉ study[6], a substudy of ASCOT

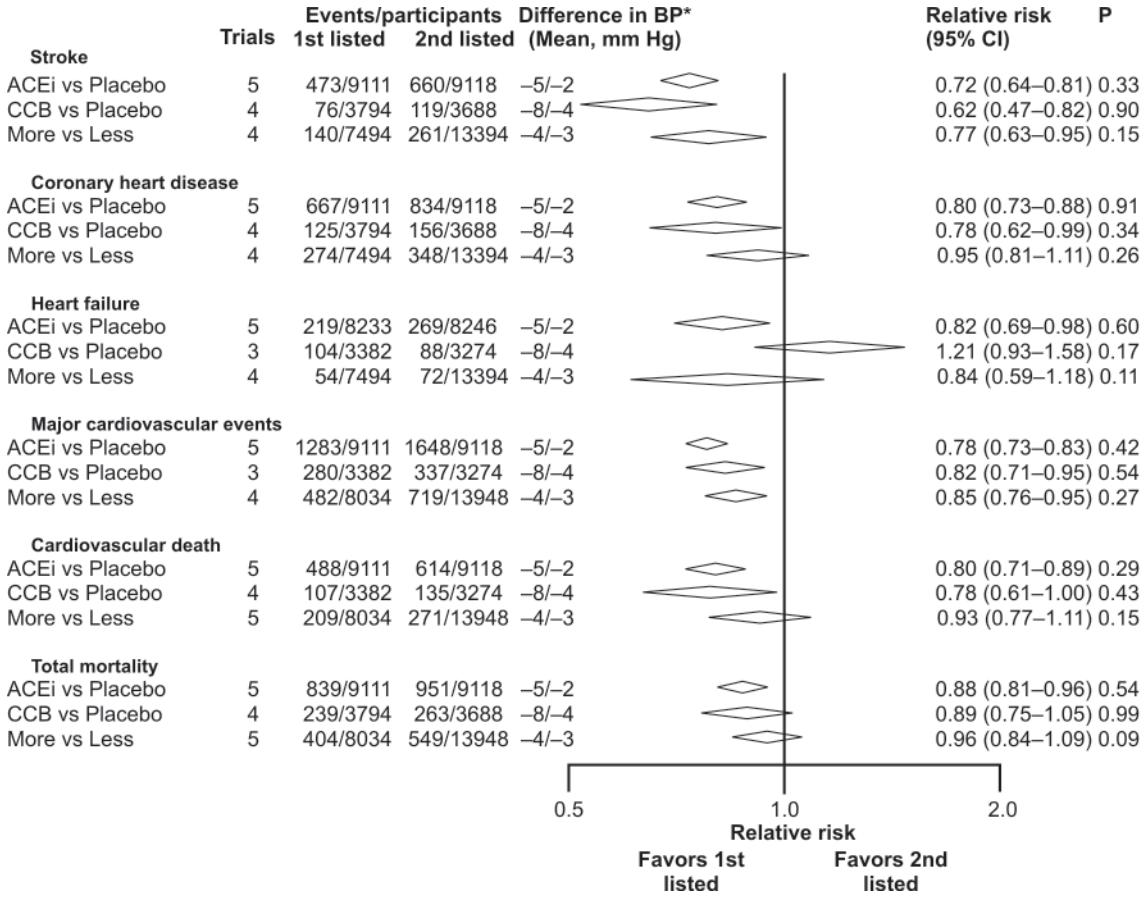


Fig. 3: Effect of ACE inhibitors and calcium antagonists vs placebo and more vs less BP lowering on cause specific cardiovascular outcomes: BP lowering treatment trialists' collaboration

study involving 2199 patients showed a greater fall in central aortic pressure with amlodipine based therapy which probably has a greater effect over stroke prevention. Compared with older drugs amlodipine-perindopril with atorvastatin reduced coronary and stroke events by almost 50%.

BP Lowering to Reduce Various Complications

Prevention of CAD: Beta-blockers are not superior to other drugs in primary prevention of CAD unlike for secondary prevention[3,8].

Stroke prevention: CCB better than ACEI (BPLTTC and NICE meta-analysis Vs HOPE and PROGRESS trials). ARBS are very good (SCOPE and LIFE trials)[8].

Heart failure prevention: The end point of HF is not an easy diagnosis to validate outside the hospital and has been a contentious issue in hypertension trials. By meta-analyses, for the treatment of hypertension, there was no evidence that ACE inhibition was more effective at preventing HF than conventional therapy. However, this conclusion is strongly influenced by the data from the ALLHAT study, which has many limitations. The ARBs appear to prevent HF almost like ACE inhibitors[8].

Impact of gender, race and ethnicity

The risk ratios did not differ with gender for any of the major outcomes, and treatment benefit is similar as well. Until recently, most trials had predominantly included white Caucasians with poor representation from black, Asian, and Hispanic patients. African-Americans blood pressure lowering response to monotherapy with drugs that inhibit the renin system, such as ACE inhibition, ARBs, or beta-blockers, as compared with CCBs or thiazide diuretics . Much less data are available for Asian patients with hypertension, but modern trials are increasingly recruiting patients from the Asia-Pacific region, which will address this

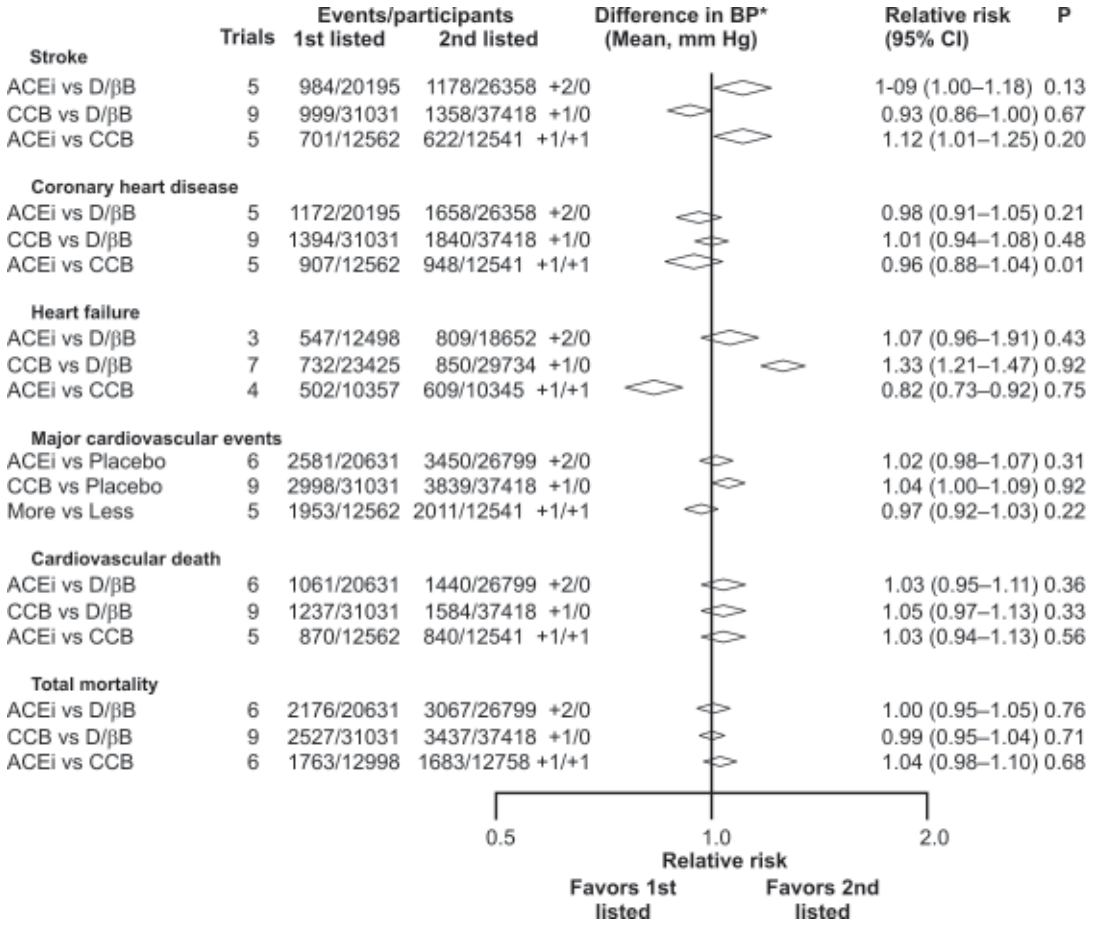


Fig. 4: Comparison of BP lowering based on drug classes, (ACE inhibitors vs Calcium antagonists): BP lowering treatment trialists collaboration

deficiency. From the limited data available, there does not appear to be any reason to anticipate major differences in drug-specific outcomes[7].

"BEYOND BLOOD PRESSURE"

A more conservative and perhaps more scientifically accurate interpretation of the data from the HOPE and EUROPA studies is that blood pressure lowering, even in those patients with seemingly "normal" blood pressures (according to the arbitrary definition of hypertension) is beneficial, especially in patients at high baseline CVD risk, and moreover, that the benefit gained is entirely consistent with that expected from the magnitude of blood pressure lowering. All meta-analysis show BP reduction is the primary factor, ASCOT –BPLA studies favor a drug specific effect beyond BP reduction.

Limitations of Present day Studies

Though they are large, well designed, randomized and blinded the clinical trials are of relatively short duration and to ensure adequate end points, trials recruit older patients at high CVD risk, often with established and severe CVD, trials are designed to assess the prevention of "events" rather than the "evolution of the disease process" that will ultimately culminate in events and younger patients are poorly represented in outcome trials. Large trials look at hard end points rather than soft or early end points like changes in resistance vessel structure, intima-medial thickness in larger arteries), left ventricular mass and structure, new-onset atrial fibrillation (AF), systemic inflammatory markers, albuminuria, and metabolic changes culminating in new-onset diabetes These studies have consistently

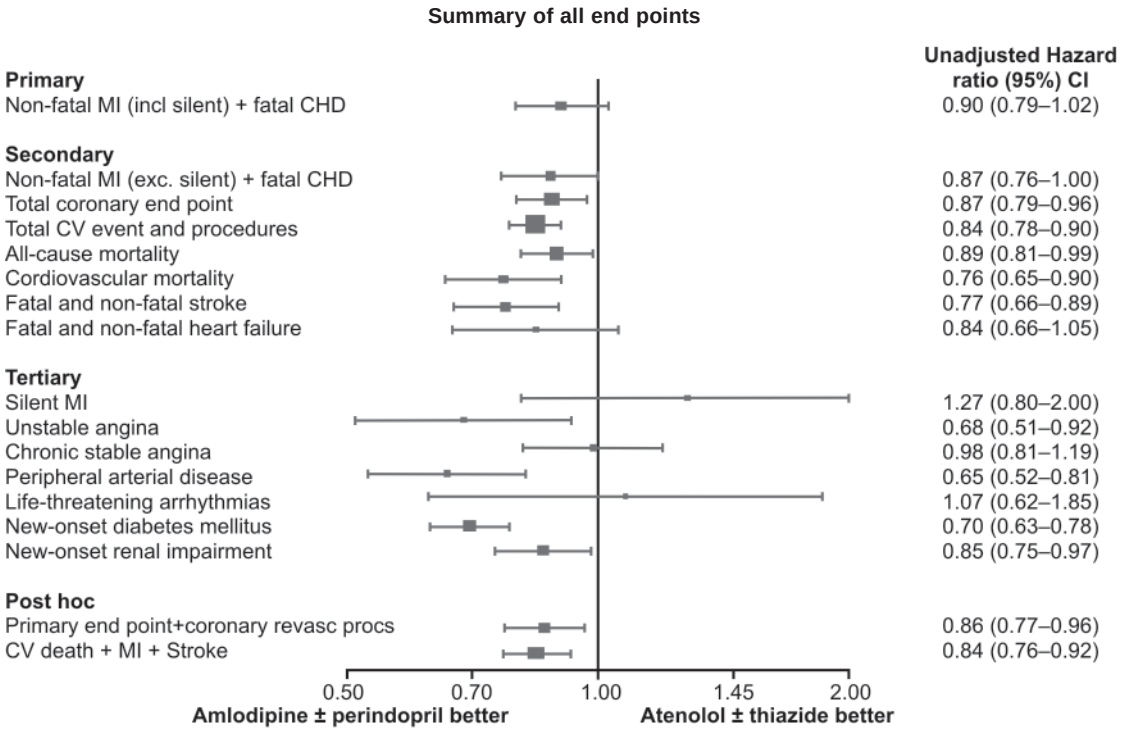


Fig. 5: ASCOT-BPLA study

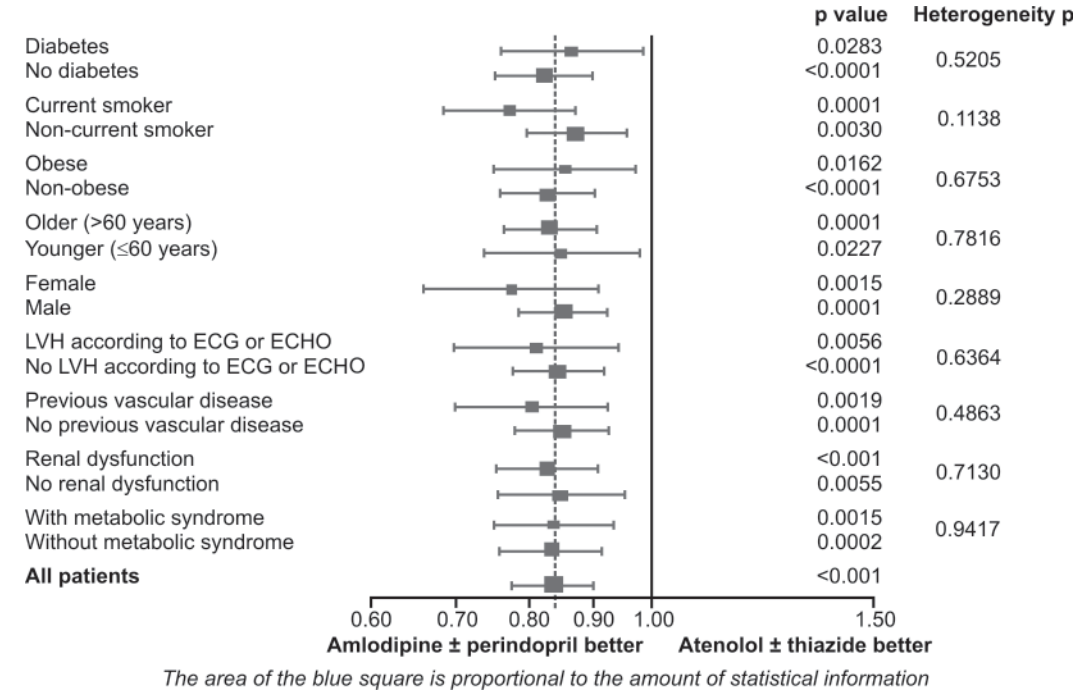


Fig. 6: Total CV events and procedures among subgroups

shown that blockade of the RAAS has favorable effects on these surrogate parameters beyond that attributable to blood pressure lowering alone.

Available data indicate that whereas ACEIs produce marked and consistent reduction of MI and CV death across diverse patient populations, the same cannot be said of ARBs. There was a 19% relative increase in MI with valsartan (compared with amlodipine) in the 15 245-patient Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial. The results of 9 of 11 key clinical trials of ARB treatment have reported an excess of MI that achieved statistical significance in 2 cases (VALUE and CHARM Alternative [the Candesartan in Heart failure Assessment of Reduction in Mortality and morbidity Alternative Trial] but the available clinical evidence and meta-analyses suggest that ARBs are indeed inferior to ACEIs with respect to MI and CV death[9].

The randomized clinical trial is as much a test of drug safety as it is of efficacy. This became important in the late 1990s when controversy first emerged about the safety of CCBs (especially short-acting CCBs) for the treatment of hypertension. This controversy was initially founded on a retrospective case-controlled study suggesting that CCBs, especially short-acting ones, may be associated with an enhanced risk of CHD, as compared with alternative treatments. Subsequently, data from a series of large, prospective, randomized, clinical trials comparing CCBs head-to-head with other blood pressure-lowering therapies, such as the Intervention as a Goal In Hypertension Treatment (INSIGHT) study, the Nordic Diliazem (NORDIL) study, ALLHAT, CONVINCE, the International Verapamil-Trandolapril Study (INVEST), and VALUE, have dismissed these concerns[8]. The ALLHAT study was specifically powered to test the CAD hypothesis as its primary end point and definitively showed effective CHD prevention with a CCB (amlodipine), including in those with diabetes. More recently, the VALUE trial further tested this hypothesis and included CAD events in its primary end point. In the VALUE trial, amlodipine was actually superior to valsartan-based therapy at protecting against fatal and nonfatal myocardial infarction (MI), as well as reducing the frequency of angina. These two very large trials confirm the conclusions from the meta-analyses, notably that, for CAD prevention, no one class of blood pressure-lowering drug has been shown to be any less or any more effective than any other; their benefits are primarily determined by how effectively they lower blood pressure[7]. The evidence is persuasive that the reduction in incidence of both MI and CV death seen with ACEIs is above that achieved by blood pressure lowering alone and is significantly greater than that achieved by ARBs in high-risk patients. All meta-analyses support the existence of an ARB-MI paradox, either by a demonstration of increased risk of coronary heart disease events or by a demonstration of a lack of blood pressure–related vascular benefits. It is truly paradoxical that 9 of

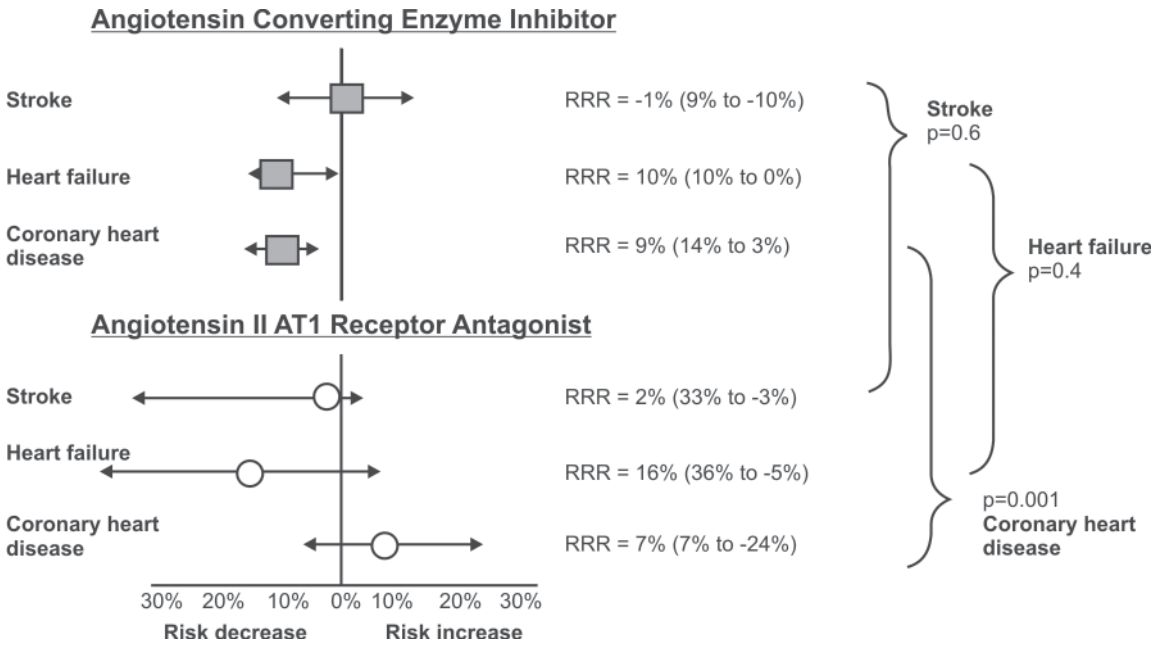


Fig. 7: ACEIs and ARBs and risk of myocardial infarction[8]

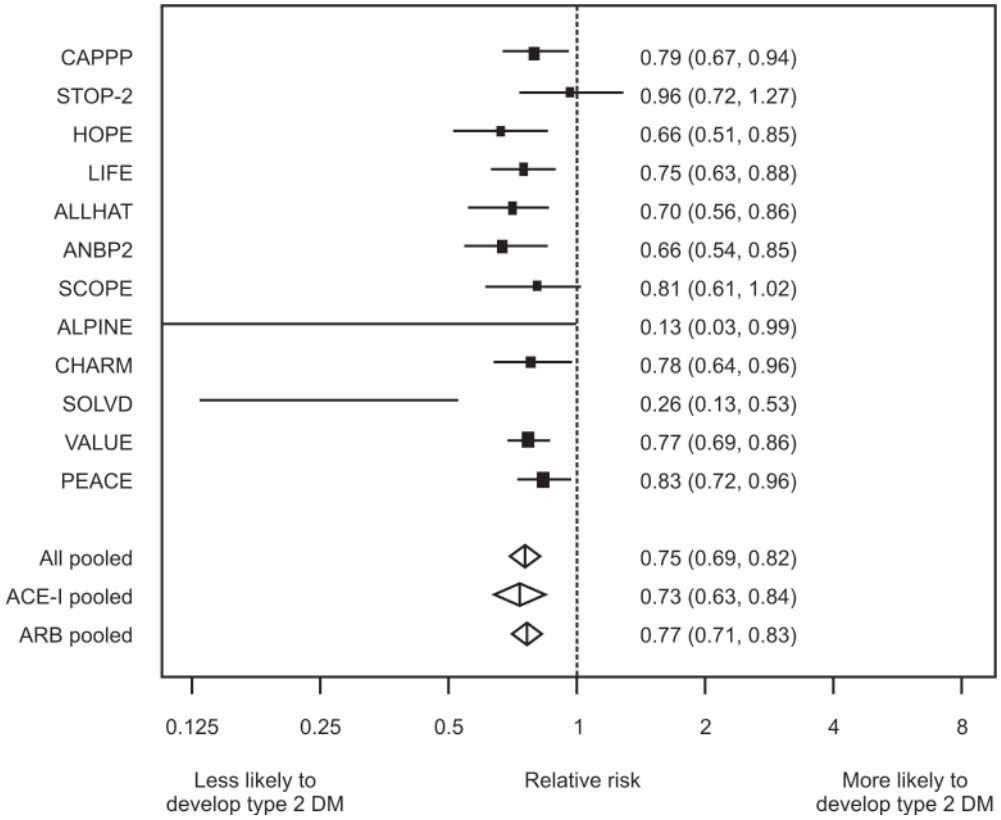


Fig. 8: Pooled risk estimates for DM with ACEI / ARB trials[9]

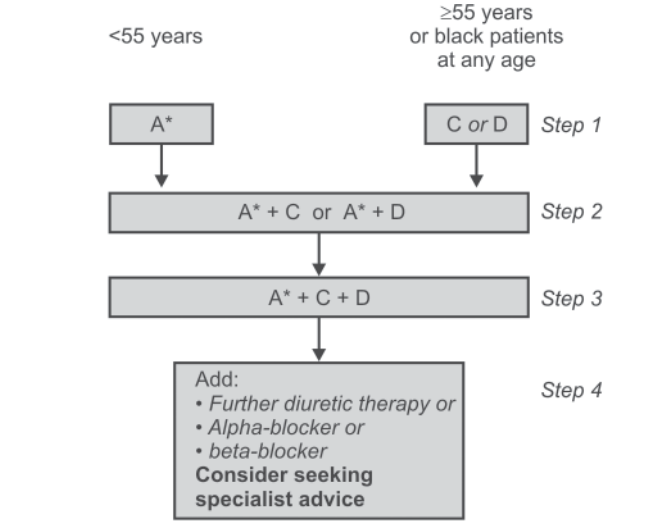
Trial (Ref. No.)	No. of Patients	Years of Follow-up*	Percent of New Diabetics	Risk Ratio (95% confidence Interval)
CAPPP	10,985	6.1	Captopril 337/5,183 (6.5%) Diuretic/beta-blocker 380/5,230 (7.3%)	0.79 (0.67–0.94)
STOP-2	6,614	5	Conventional drugs 97/1,961 (4.9%) ACE inhibitors 93/1,969 (4.7%)	0.96 (0.72–1.27)
HOPE	9,297	5	Ramipril 102/2,837 (3.6%) Placebo 155/2,883 (5.4%)	0.66 (0.51–0.85)
LIFE	9,193	4.8	Losartan 241/4,019 (6%) Atenolol 319/3,979 (8%)	0.75 (0.63–0.88)
ALLHAT	33,357	4.9	Lisinopril 119/4,096 (8.1%) Chlorthalidone 302/6,766 (11.6%)	0.70 (0.56–0.86)
ANBP2	6,083	Median 4.1	Enalapril 138/2,800 (4.9%) HCTZ 200/2,826 (7.1%)	0.66 (0.54–0.85)
SCOPE	4,937	3.7 Maximum 5	Candesartan 93/2,167 (4.3%) Placebo 115/2,175 (5.3%)	0.81 (0.61–1.02)
ALPINE	392	1	Candesartan ± felodipine 1/196 (0.5%) Atenolol ± HCTZ 8/196 (4%)	0.13 (0.03–0.99)
CHARM	7,599	3.2	Candesartan 163/2,715 (6%) Placebo 202/2,721 (7%)	0.78 (0.64–0.96)
SOLVD	4,228	3.4	Enalapril 9/153 (5.9%) Placebo 31/138 (22.4%)	0.26 (0.13–0.53)
VALUE	15,245	4.2	Valsartan 690/5,267 (13.1%) Amlodipine 845/5,152 (16.4%)	0.77 (0.69–0.86)
PEACE	8,290	Maximum 7 Median 4.8	Trandolapril 335/3,432 (9.8%) Placebo 399/3,472 (11.5%)	0.83 (0.72–0.96)

Fig. 9: Prevention of diabetes by ACEI / ARB[9]

the 11 key ARB trials showed an excess in rates of MI, an observation that is difficult to discount in Clinical practice (Fig. 7). Discussion will continue as ongoing trials such as ONTARGET/TRANSCEND (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE intolerant subjects with cardiovascular Disease) provides further comparative information.

NEW-ONSET DIABETES: IMPACT OF BLOOD PRESSURE-LOWERING DRUGS

Diabetes is reaching epidemic proportions in westernized societies, and hypertension and diabetes are a lethal duo. Conventional therapy (i.e., thiazide and/or betablocker), especially when combined, is associated with the highest rate of new diabetes. Blockade of the renin system with ACE inhibition or ARBs appears to be associated with the lowest rate of new diabetes, with CCBs sitting between the two extremes[10]. In HOPE study was diabetes reduced by 34%. A meta-analysis of 12 Randomized trials showed reduced risk of diabetes with ACE inhibitors (27%) and ARBs (23%). (Fig. 6)[10]. The DREAM trial,[11] did not show any reduction in new onset diabetes with ramipril at 3 years though there was increased regression to normoglycemia .The discrepancy between meta analysis and DREAM study could be due to specifically designed vs posthoc analysis, different baseline patient characteristics and shoter duration of study in DREAM (3 years in 4.5 in meta analysis). We have to await results of 2 ongoing trials (NAVIGATOR-Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research, and ONTARGET/TRANSCEND- Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease. As of now Antihypertensives drugs can not be recommended for sole purpose of preventing diabetes, but they may offer some protection against new onset diabetes.



A= ACE inhibitor (*or ARB if ACEi-intolerant); C=Calcium-channel blocker; D=thiazide-type diuretic, Beta-blockers are not a preferred initial therapy for hypertension but are an alternative to A in patients <55 years in whom A is not tolerated, or contraindicated (includes women of child-bearing potential). Black patients are only those of African or Caribbean descent. In the absence of evidence, all other patients should be treated according to the algorithm as non-black.

Fig. 10: BHS/NICE guidelines 2006

The key debate over the next few years will not be whether one class of blood pressure-lowering drug is better than another, but rather what is the most effective therapeutic strategy to reduce the overall CVD risk burden of individual patients. After all, the purpose of treatment is to reduce the risk of stroke and CHD, not just control of blood pressure! .In fact, considering that multidrug therapy is now required in almost all hypertensive patients, the argument as to which initial therapy is associated with the best results is virtually moot.

BHS/NICE guidelines released in June 2006,[12] based on all relevant data available till end of 2005, relegate betablockers to a back stage. It differentiates below and above age 55. Beyond 55 the primary concern is stroke prevention with emphasis on systolic BP. Below age 55, primary target cardiac risk, where the guideline states therapy should begin with ACE inhibitors or ARBs (though there is a paucity of data from clinical studies in young hypertensives). Still, beta-blockers have a definite role in young women of childbearing potential, where ACEI/ARBs are contraindicated and in patients with CAD, heart failure and hyperadrenergic states.

Target blood pressures for various disease states are as follows: no associated risk factor: 140/90 mm Hg: diates, heart or renal failure 130/80 mm Hg. In the present day management of hypertension aggressive control of blood pressure as well as other risk factors will reduce the global cardiovascular risk. The choice of agent is of relatively less significance,where probably newer classes offer an edge over the traditional drugs namely beta-blockers and diuretics in the United States; Circulation 2005; 112: 1651-1662

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