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Antihypertensive Medications: Benefits of BP Lowering and Hazards of Metabolic Effects

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Abstract

Blood pressure reduction is associated with significant reduction in adverse cardiovascular outcomes. Certain blood pressure lowering drugs have adverse effects on glucose homeostasis, and have been associated with development of both pre-diabetes and diabetes during use. There is controversy over the significance of diabetes that develops during treatment with antihypertensives and whether the benefits of blood pressure reduction offset the hazards of dysglycemia that can lead to diabetes. Many hypertension treatment guidelines have recently undergone revisions to include consideration for the metabolic effects of antihypertensive drugs, particularly in high risk populations. This review summarizes the data related to the benefits of blood pressure reduction as well as the adverse metabolic effects and new onset diabetes associated with some antihypertensive medications.

Keywords

Hypertension; Diabetes; Pre Diabetes; Thiazide Diuretics; β blockers; New Onset Diabetes; Cardiovascular Outcomes

For almost as long as thiazide diuretics and β blockers have been available, there has been concern over their metabolic effects. While in some cases these concerns have lead to preferential prescribing of other antihypertensive drug classes to avoid the adverse metabolic effects (AMEs), in others, the concerns are ignored in favor of their blood pressure (BP) lowering effects. There is no question that thiazide diuretics and β blockers lower BP, which in turn reduces risk for adverse cardiovascular (CV) outcomes. However, the potential hazards of the AMEs associated with these antihypertensive classes, the most serious of which is diabetes, has stimulated debate over the best choice of initial antihypertensive medication, particularly in patients at risk for developing diabetes. In this review we will present data summarizing the benefits of BP reduction with regard to reduced CV adverse outcomes as well as dysglycemia, defined as the dysfunction of blood glucose metabolism, as they relate to various antihypertensive medication classes.

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BP Reduction and CV Risk

The public health burden related to the morbidity and mortality of hypertension is enormous and increasing. For an individual who is normotensive at age 55 years, the lifetime probability of developing hypertension is 90%. [1] The relationship between BP and CV disease events is continuous and consistent, and independent of other risk factors. [2] A 10 year, 12 mmHg decrease in BP results in the prevention of 1 death for every 11 patients treated, [2] and every 20 mmHg incremental increase in systolic BP (10 mmHg increase in diastolic BP) doubles the risk of CV disease. [3] The benefits of BP reduction on overall mortality and CV outcomes are observed throughout the latter half of a patient's life [3] and regardless of sex. [4] Antihypertensive therapy is associated with a 35–40% reduction in stroke, 20–25% decrease in myocardial infarction (MI), and greater than 50% reduction in heart failure (HF). [5]

The benefits of BP reduction following antihypertensive therapy is no longer questioned, however there is still some debate with regard to the relative efficacy of antihypertensive drug classes. The early landmark placebo-controlled BP trials demonstrated significant reduction of CV morbidity and mortality associated with BP lowering, primarily with thiazide diuretics and older β blockers. [6–15] More recently, BP trials have focused on the relative efficacy of newer antihypertensive agents, including angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs) versus older antihypertensive agents (thiazide diuretics and β blockers). [16–23] Even more recently, major trials have assessed combination therapies, owing to the usual necessity of a multi-drug regimen to provide adequate blood pressure lowering. [24–29] The Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial, published late last year evaluated initiating BP lowering therapy with either the combination of benazepril+amlodipine or benazepril+HCTZ. [26] The benazepril+amlodipine combination resulted in significantly better BP reduction as well as significantly reduced risk of CV adverse outcomes, both in the whole cohort and in the cohort with diabetes.

These studies are summarized in Table 1 and, in general, indicate that when compared to placebo, treatment with antihypertensive therapy significantly reduces CV adverse outcomes, and there is little difference in adverse outcomes when individual or combination agents are compared. These data provide some of the most compelling evidence in modern medicine that treating a mostly asymptomatic disease, regardless of the class of antihypertensive agent(s) used, profoundly impacts long-term morbidity and survival.

Thiazide Diuretics

Thiazide diuretics have been the gold standard of antihypertensive therapy in most outcome trials and remain a first line recommendation for treating uncomplicated hypertension in the US and Europe. [30,31] In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the authors conclude that thiazide-type diuretics are superior in preventing one or more major forms of CV disease and should be preferred as initial antihypertensive therapy. [20] While ALLHAT and a meta-analysis [32] suggests the superiority of thiazide diuretics over other BP lowering agents in terms of adverse CV outcome reduction, the majority of clinical trial evidence shows that, in uncomplicated hypertension, little additional benefit exists between antihypertensive agents with respect to overall CV outcomes which are driven by BP reduction. [16–18,21,22,33] There is evidence to support the use of thiazide diuretics in many patient populations, in head to head comparisons with other antihypertensives, and in combination with other antihypertensive agents. For these reasons, thiazide diuretics have been recommended as initial therapy for most patients with uncomplicated hypertension in clinical guidelines. [30,31,34]

β Blockers

Many clinical trials have shown β blockers to be effective agents for BP lowering as well as reduction of adverse CV outcomes in comparison to thiazide diuretics and newer agents, [8, 13,14,18,22,35–37], and have been included as first line hypertension treatment in US guidelines since the early 1980s.[38] More recently, β blockers have fallen out of favor as a first line agent for BP reduction, due in part to questions about their tolerability and safety as a means of stroke prevention.[39,40] However, β blockers play an important role in conventional antihypertensive therapy, as they are useful in the management of hypertension, ischemic heart disease and arrhythmias,[30] and have shown benefits in patients who have had an MI[41,42] or HF.[43–45] The 2007 American Heart Association guidelines for the management of hypertension recommend that β blockers should only be first line therapy for the treatment of hypertension in patients with angina, prior MI, or HF.[34] The heterogeneity of the β blocker class of antihypertensives is evident in the treatment of HF, and the newer long-acting β blockers and β blockers with vasodilating properties have been shown most beneficial.[43,46–48]

Renin Angiotensin System Blocking Agents and Calcium Channel Blockers

Large BP lowering and CV outcomes trials have provided convincing evidence that ACEIs and ARBs provide CV benefit in a variety of populations including those with hypertension, HF, previous MI or stroke, diabetes, and renal disease.[20,36,49–54] However, Calcium Channel Blockers (CCBs) and thiazide diuretics have been shown to produce better BP reduction than RAS blocking agents in elderly and black populations.[55–57]

Diabetes and CV Disease Risk

Diabetes is a global public health concern associated with an estimated annual cost of \$174 billion in the United States alone.[58] The World Health Organization (WHO) predicts that by the year 2030, 350 million individuals worldwide will have diabetes.[59] Diabetes increases CV risk without regard to other risk factors, including all levels of BP,[52,60,61] and accordingly, has been designated a CV disease risk equivalent according to National Cholesterol Education Program Adult Treatment Panel.[62] Even pre diabetes, defined as impaired fasting glucose (IFG, 100–125 mg/dL) or impaired glucose tolerance (IGT, 2 hour oral glucose tolerance test (OGTT) 140–199 mg/dL), increases CV risk,[63,64] suggesting that the inherent CV risks with elevated glucose begin early in the diabetes continuum. Pre diabetes also increases the absolute risk of developing diabetes by 3–10 fold.[63–65] Early identification and treatment of patients with pre diabetes has potential to reduce or delay progression to diabetes, related CVD, and microvascular disease.[66]

Several guidelines suggest lower BP goals ($\leq 130/80$ mm Hg), in diabetic and pre diabetic patients.[30,31,34,66] Thiazide diuretics, β blockers, ACEIs, ARBs, and CCBs are beneficial in preventing major CV outcomes in diabetic patients with hypertension, although when compared to those without diabetes, risk for CV outcomes in diabetics is significantly higher. [19,20,36,67] There is some evidence that ACEIs and ARBs provide additional CV morbidity and mortality benefit in patients with diabetes beyond BP reduction [50,52,68,69] and they are recommended as a component of first-line hypertension treatment in those with diabetes.[30] RAS blocking agents also have favorable effects on the progression of diabetic and non-diabetic kidney disease,[49,70–72] and are now recommended as first line BP lowering agents in those with pre diabetes.[66]

Antihypertensive-Associated New Onset Diabetes

Thiazide diuretics and β blockers adversely affect glucose homeostasis, which has lead to a reproducible association with new onset diabetes (NOD) in large scale clinical trials. Some

studies have observed very small or no absolute differences in NOD between major antihypertensive drug classes.[22,73] This may be explained by the fact that these populations were at relatively low risk for diabetes development.[74] Many other large, prospective clinical trials have shown significant differences in the rates of NOD for those treated with thiazide diuretics and/or β blockers compared with ACEIs, ARBs and CCBs alone or in combination. Data from these trials are summarized in Table 2. ACEIs and ARBs are generally regarded as agents that reduce the risk for NOD, CCBs as metabolically neutral, and β blockers and thiazide diuretics as agents that increase the risk for NOD.[75] A recent meta-analysis by Elliott et al. confirmed the generally regarded rank order of these drug classes and observed that of all antihypertensive drug classes, thiazide diuretics and β blockers confer the greatest risk for NOD, and showed β blockers have the same risk for NOD as thiazide diuretics.[76]

Possible physiologic mechanisms explaining the metabolic effects of the RAS blocking agents, thiazide diuretics and β blockers are summarized in Table 3.[77,78]

Renin Angiotensin System Blockers

The decreased incidence of NOD with ACEIs and ARBs compared to β blockers and/or thiazide diuretics has been demonstrated in several major CV outcomes and BP trials.[20,21,53,79, 80] RAS blocking agents have also been shown to prevent NOD during antihypertensive therapy compared to placebo.[52,81] Several meta-analyses have confirmed reductions in NOD with ACEIs and ARBs, suggesting an approximate 20% relative reduction in NOD compared to other agents.[82–85] More recently the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial, which included NOD in their primary endpoint analysis, failed to show a statistically significant reduction in NOD with the ACEI ramipril versus placebo in patients with IFG.[86] DREAM is the first trial to prospectively evaluate reduction of NOD with an ACEI as the primary endpoint. However, the DREAM trial was not conducted in a hypertensive population and there was a significant regression of glucose to normoglycemia in those with with ramipril after 2 years. Although the DREAM trial challenges results regarding NOD from major landmark hypertension trials, the lack of hypertension as an inclusion criterion in the DREAM trial results in a population at lower risk for diabetes development over the relatively short follow up period (3 years), which may not have been sufficient to observe a statistical difference in NOD. The Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial is a large, prospective trial which tests the use of the ARB valsartan as well as nateglinide in a 2×2 factorial design, in patients who have IGT but who also have, or at high risk for heart disease. [87] The primary outcomes of NAVIGATOR are the development of diabetes and development of cardiovascular morbidity and mortality. Data from NAVIGATOR should be available in the near future, and will shed additional light on the ability of RAS blockade to reduce the risk of diabetes.

Calcium Channel Blockers

CCBs are generally considered to have little or no impact on glucose regulatory pathways. Meta analyses and systematic reviews have indicated that CCBs are associated with less NOD than β blockers and thiazide diuretics, but more NOD than ACEIs and ARBs.[76,82,85] The Intervention as a Goal in Hypertension Treatment (INSIGHT) trial observed an decreased risk of NOD with nifedipine versus co-amlozide,[17] whereas the Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial observed a decreased risk of NOD with valsartan compared with amlodipine.[88] The International Verapamil SR-Trandolapril Study (INVEST) found a reduced risk of NOD with the verapamil SR + trandolapril strategy compared with atenolol + HCTZ strategy,[89] and in the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) there was a reduced risk of NOD in the amlodipine + perindopril strategy compared with the atenolol + bendroflumethiazide strategy.[90]

Thiazide Diuretics

While the exact mechanism of thiazide diuretic induced BP reduction is not known, it is thought to be associated with an initial reduction in plasma and extracellular fluid volume as well as a reduction in renal perfusion and activation of the RAS. Many of the physiological mechanisms of thiazide diuretics which are thought to be associated with dysglycemia and NOD involve decreased vascular perfusion, upregulation of the RAS, and elevated angiotensin II (Ang II) (Table 3). Potassium homeostasis also appears to play an important role in the mechanism by which thiazide diuretics impair carbohydrate metabolism through actions which blunt the release of insulin from the pancreas.[91] An inverse relationship between serum potassium and glucose levels following treatment with thiazide diuretics was observed in a meta analysis by Zillich et al.[92] Potassium supplementation in patients with thiazide-induced hypokalemia can lower blood pressure and may improve dysglycemia,[93,94] however this has not been prospectively evaluated in large numbers of patients or for long term effects.

Many major antihypertensive trials have observed increases in NOD with the treatment arm that included a thiazide diuretic either alone or in combination with a β blocker.[17,20,24,37, 53] Several meta-analyses have also confirmed increased incidences of NOD compared to other antihypertensive classes.[76,82–85] It should be noted that discontinuation of thiazide diuretics can result in decreased glucose and improved glucose tolerance.[95,96]

The development of NOD with thiazide diuretics may also be dose related, as higher doses are more likely to be associated with NOD.[91] Several clinical trials have used what would be considered medium to high doses of thiazides,[97] such as 50 to 100mg of chlorthalidone, [12] or 25 mg hydrochlorothiazide (HCTZ).[17,24] Lower doses of thiazide diuretics can be tried to reduce the risk of dysglycemia in at risk populations, however BP should be monitored and additional drugs added as necessary.

β Blockers

The mechanism of β blocker induced NOD may result from a combination of changes in lipoprotein lipase activity, reduced insulin secretion, weight gain, and peripheral vasoconstriction from unopposed α adrenergic activity.[98] β blockers have been associated with increased incidence in NOD compared with other antihypertensives.[21,76,79,99] In one cohort study Gress *et al* found an increase in NOD with β blockers, but not with thiazides. [100] Although nonselective β blockers or higher dose selective β blockers have been shown to be associated with greater risk for AMEs,[101] newer β blocking agents with vasodilating activity such as carvedilol may not be.[102] Compared with metoprolol, carvedilol has been associated with a decreased risk of NOD in patients with HF[103] and an improvement in hemoglobin A1c in hypertensive diabetes.[104]

Combination Therapy

The evaluation of clinical trials that employ combination antihypertensive treatment strategies for BP lowering is particularly important since most hypertensives, especially diabetics, require at least two antihypertensive agents to adequately control BP.[29] Most of these trials have pitted the efficacy of older antihypertensive agents (β blockers plus thiazide diuretics) versus newer agents (CCB plus ACEIs/ARBs) and the results have indicated increased NOD with older therapies.[89,90,105] A cohort study by Burke et al. found that combination therapies that included an ACEI had lower incidences of NOD, and that the risk of NOD was lowest with ACEI and thiazide combination therapy.[106]

Overall, differences in study design, follow up period, sample size, patient populations, diabetes definition, antihypertensive agents and dose, and BP lowering in the comparison groups make direct comparisons and interpretation of NOD between trials difficult. The most

compelling evidence that there are varying rates of NOD with different antihypertensive classes comes from analyses of trials that were designed and powered to observe difference in CV outcomes related directly to BP reduction but which had NOD pre-specified as a secondary outcome. Prevention of NOD has been identified as a primary outcome in ongoing investigation, and may provide important additional information that fill in gaps in our current understanding of antihypertensive induced NOD.[107]

New Onset Diabetes and CV Outcomes

Since diabetes and IFG confer increased CV risk, it has been argued that older antihypertensive agents should be avoided in those at risk for development of diabetes, despite their CV benefit. [75,108] However, others argue that antihypertensive-induced NOD is an "innocent" condition. [109] The controversy is fueled by a paucity of CV outcome data associated with NOD. The evidence for CV outcomes with antihypertensive-related NOD is summarized at the bottom of Table 2.

An observational study of hypertensives treated primarily with thiazide diuretics and β blockers and followed for 25–28 years, showed a greater risk of stroke, MI, and mortality in those who developed NOD.[110] Other observational studies with shorter follow up have shown non-significant trends of increased CV risk associated with NOD. [111,112] Dunder *et al* found that a rise in blood glucose between 50 and 60 years of age predicted MI after 17.4 years of follow in a population men treated with HCTZ and β blockers compared with those not receiving HCTZ and β blockers.[113] An analysis of the Multiple Risk Factor Intervention Trial (MR FIT) also revealed increased CV risk with diabetes developed during antihypertensive therapy.[114] In an observational study by Verdecchia *et al* of hypertensives followed for up to 16 years, the incidence of CV events was the same comparing those who had diabetes at baseline and those who developed NOD during treatment with antihypertensive, and was significantly higher compared with those who never developed diabetes.[115] Baseline glucose and diuretic use were independent predictors for NOD. Similarly, a posthoc analysis of the Systolic Hypertension in the Elderly Program (SHEP) observed an increase in CV outcomes and total mortality in those who developed NOD after 14.3 years of follow up. [116] In an analysis of ALLHAT, while there was an increase in coronary heart disease risk, there was no significant increase of CV mortality associated with NOD[117], but follow up was likely too short to observe a difference.[75]

In an analysis of the VALUE trial, NOD was associated with a 43% higher risk of cardiac morbidity compared to those who did not develop diabetes after 4.2 years of follow up. In addition, the analysis of VALUE data suggested an intermediate CV risk associated with NOD compared to subjects with and without diabetics at study entry.[118] A similar incremental risk was observed in several of the aforementioned studies.[110,112] This incremental CV risk observed in those who develop NOD is consistent with an early stage of diabetes progression and supports the notion that there is a lag between the time pre diabetes and/or diabetes is diagnosed and the development of adverse CV outcomes.[66]

Together with the evidence that diabetes of other etiologies significantly worsens long term CV morbidity and mortality, this evidence that patients with NOD are also at increased risk for long term adverse outcomes, particularly when follow up is extended, is not surprising. However, it has been argued that there is not a direct association between thiazide diuretic or β blocker induced NOD and adverse outcomes.[119] Outcome data from large hypertension treatment trials provide strong evidence of the CV benefits, even in the presence of metabolic abnormalities, and at this time, the prognostic impact of NOD that is directly associated with antihypertensives is not clear. Lack of direct supporting evidence of a drug:NOD:CV outcome relationship may be due to inadequate statistical power which may have impeded such an

observation,[120] as BP-lowering clinical trials have not been designed *a priori* for assessment of this relationship. The lack of clarity in the evidence for CV outcomes in antihypertensive-associated NOD underscores the need for adequately powered hypertension treatment trials which prospectively evaluate the long term effects of NOD.

In evaluations of antihypertensive associated NOD, predictors of NOD, such as IFG and increased BMI, race, and age, tend to be similar to predictors of diabetes of other etiologies, [79,89,121–123] and implies that NOD during treatment with antihypertensives can be predicted to occur in patients already at risk for diabetes. It may therefore be beneficial to avoid thiazide diuretics and β blockers in patients with IFG, increased BMI or waist circumference and other conditions known to increase the risk for development of diabetes.[75,115]

Conclusion

Choice of antihypertensive agent(s) is a clinical decision based on many factors, including an individual patient's BP, BP goal, and risk conditions such as HF, prior MI, classic angina, and edema. Consideration should be given not only to the benefits of BP lowering which are well established and not in dispute, but also to the metabolic risks of some BP lowering drugs. There are clear cardiovascular outcome benefits as a result of BP lowering. It is less clear what the impact of new onset diabetes is with regard to long term macrovascular complications. However, as the prevalence of hypertension in those at risk for diabetes increases, it is important to bear in mind the metabolic consequences of antihypertensive medications. If thiazide diuretics and/or β blockers are agents of choice based on an individual patient's clinical characteristics, then the lowest possible dose and close monitoring should be employed in order to recognize and manage metabolic adverse outcomes early on, while still maintaining adequate BP control.

Expert Commentary

In the last few years many professional societies have revised guidelines and recommendations for treatment of hypertension based on data summarized in this review. The European Society for Hypertension/European Society of Cardiology are no longer endorsing thiazide diuretics or β -blockers in hypertensive patients with diabetes[31] and the American Association of Clinical Endocrinologists recommends thiazide diuretic use only at low dosage and only with adequate potassium replacement and β -blocker use only as second- or third-line agents in patients with diabetes.[124] The National Institute for Health and Clinical Excellence, together with the British Hypertension Society, recently published guidelines that indicate β -blockers are no longer a suitable first-line treatment option in uncomplicated hypertensive patients largely due to increased incident diabetes and they recommend use of RAS inhibitors as first-line therapy in younger patients, with diuretics reserved for the elderly or black patients of any age.[125] Although thiazide diuretics are an inexpensive therapeutic option for treating hypertension, risk of diabetes and the long term associated complications should be carefully considered and may outweigh the immediate cost savings.

Five Year View

Obesity and physical inactivity continue to increase and are major factors influencing prevalence of pre diabetes, metabolic syndrome, diabetes and hypertension. Of significant concern is the rapidly growing population of children and adolescents with these conditions. Better understanding the long term metabolic and associated CV risks following use of antihypertensive agents is increasingly important as the population in whom they are used gets younger and the duration of required treatment gets longer.

As part of its strategic plan, the National Heart Lung and Blood Institute (NHLBI) has recently embarked on new guideline efforts by constituting committees aimed at developing evidence-based, comprehensive, integrated clinical guidelines for CV risk reduction directed principally at primary care practitioners to help adult patients reduce their risk for CV disease. Concurrent with this process, NHLBI will update existing guidelines on the prevention, detection, evaluation and treatment of high blood cholesterol/dyslipidemia (ATP III), hypertension (JNC 7) and overweight/obesity (Obesity Guidelines). These new guidelines will likely consider much of the data and issues discussed in this review, and will shape treatment recommendations of hypertension and other CV risk conditions not only in the US, but worldwide in the next five years.

Key Issues

- Hypertension is associated with increased cardiovascular risk and reducing blood pressure with antihypertensive agents significantly decreases that risk
- Diabetes is often associated with hypertension and imparts even greater risk for cardiovascular outcomes than hypertension alone
- Thiazide diuretics and β blockers, classes of medication commonly used to treat hypertension, have been associated with an increased risk new onset diabetes due to their adverse effects on glucose and insulin homeostasis
- When long term follow up is available, new onset diabetes has been shown to increase cardiovascular risk similarly to diabetes of other etiologies
- When selecting antihypertensive medications for patients with or at risk for pre diabetes and metabolic syndrome, consideration should be given not only to the BP lowering effects, but also the adverse metabolic effects of the medications in order to prevent or delay the development of diabetes

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Table 1

Study, Year	Mean Follow Up (Years)	Population	Drug Therapy (Sample Size)	BP Reduction (Systolic / Diastolic) at Study End	Outcomes Benefit (Primary composite endpoint)	Risk Ratio (Hazard or Odds Ratio)
ANBPS, 1980 [6]	4.0	Age 30–69, mild hypertensive	HD Chlorothiazide (1721) Placebo (1706)	12.2 mmHg (diastolic) 6.6 mmHg	Death and non-fatal CV events	0.80, $p < 0.05$
HDFFP, 1982 [9]	5.0	Age 30–69, mild hypertensive	HD Chlorthalidone (5485) Placebo (5455)	N/A	Five Year Mortality	1.5 (0.39–2.61)
MR FIT, 1982 [12]	7.0	Age 35–57, high risk hypertensive	Chlorthalidone (6,428) Placebo (6,438)	10.5 mmHg (systolic) 7.3 mmHg	CHD mortality	0.93 (0.75–1.15)
MRC, 1985 [8]	4.9	Age 35–64, mild hypertensive	bendrofluzide (4297) Propranolol (4403) Placebo (8654)	11/6 mmHg 9/6 mmHg N/A	All CV events (stroke, coronary events, and death due to CV causes)	0.81 (0.69–0.95) (active vs placebo)
SHEP, 1991 [15]	4.5	Age > 60, ISH	Chlorthalidone ± atenolol (2365) Placebo (2371)	27/9 mmHg 15/5 mmHg	Nonfatal and fatal stroke	0.64 ($P = .0003$)
STOP, 1991 [13]	2.1	Age 70–84, hypertensive	Diuretics or β Blockers (812) Placebo (815)	29/17 mmHg (combined) 2/7 mmHg	MI, stroke, CV death Mortality	0.60(0.43–0.85) 0.57(0.37–0.87)
MRC, 1992 [14]	5.8	Age 65–74, untreated hypertensive	HCTZ/amiloride (1081) Atenolol (1102) Placebo (2213)	24/20 mmHg (combined) 10/9 mmHg	Stroke, coronary events, all cause death	0.83 (0.71–0.98) (active vs placebo)
SYST-EUR, 1997 [23]	2.5	Age ≥ 60, ISH	Nitrendipine (2398) Placebo (2297)	23/7 mmHg 13/2 mmHg	Fatal and non-fatal stroke	0.58 (0.40–0.83)

Study, Year	Mean Follow Up (Years)	Population	Drug Therapy (Sample Size)	BP Reduction (Systolic / Diastolic) at Study End	Outcomes Benefit (Primary composite end point)	Risk Ratio (Hazard or Odds Ratio)
HAPPHY, 1987 [35]	3.8	Hypertensive Men, Age 40–64	Thiazide Diuretics (3272) β Blockers (3297)	26/18 mmHg 26/19 mmHg	CHD events, Stroke, Mortality	1.00 (0.83–1.21)
VHAS, 1997 [16]	2.0	Age 40–65, hypertensive	Verapamil SR (707) Chlorthalidone (707)	28/17 mmHg 29/17 mmHg	CV Events (All Cause death, MI, stroke, TIA, HF)	0.98, NS
CAPP, 1999 [21]	6.1	Age 25–66, hypertensive	Captopril (5492) β Blockers or Diuretics (5493)	15/10 mmHg 15/10 mmHg	Fatal and non-fatal MI, stroke, and other CV deaths	1.05 (0.90–1.22)
STOP-2, 1999 [22]	5.0	Age 70–84, hypertensive	DHP CCB (2196) ACEI (2205) β Blockers or Diuretics (2213)	35/18 mmHg 35/17 mmHg 36/15 mmHg	Fatal stroke, fatal MI, and other CV mortality	0.99 (0.84–1.16) (newer vs older agents)
INSIGHT, 2000 [17]	3.5	Age 55–80, hypertensive plus 1 CV risk factor	Nifedipine (3157) HCTZ+amiloride (3164)	33/17 mm Hg 33/17 mmHg	CV death, MI, HF, or stroke	1.10 (0.91–1.34)
NORDIL, 2000 [18]	4.5	Age 50–74, hypertensive	Diltiazem (5410) β Blockers or Diuretics (5471)	20/19 mmHg 23/19 mmHg	Fatal and non-fatal stroke, MI, and other CV death	1.00 (0.87–1.15)
LIFE, 2002 [19]	4.7	Age 55–80, hypertensive with LVH	Losartan (4605) Atenolol (4588)	30/17 mmHg 29/17 mmHg	Primary CV event (death, myocardial infarction, or stroke)	0.87 (0.77–0.98)
ALLHAT, 2002 [20]	4.9	Age ≥ 55, hypertensive with high CV risk	Chlorthalidone (15255) Amlodipine (9048) Lisinopril (9054)	12/9 mmHg 11/9 mmHg 10/9 mmHg	Combined fatal CHD or nonfatal MI	0.98 (0.90–1.07) 0.99 (0.91–1.08)
ANBP2, 2002 [53]	4.1	Age 65–84, hypertensive	ACEI (3044) Diuretics (3039)	26/12 mm Hg 26/12 mmHg	CV events or deaths	0.89 (0.79–1.00)

Mono-therapy Trials

Study, Year	Mean Follow Up (Years)	Population	Drug Therapy (Sample Size)	BP Reduction (Systolic / Diastolic) at Study End	Outcomes Benefit (Primary composite endpoint)	Risk Ratio (Hazard or Odds Ratio)
INVEST, 2003 [24]	2.7	Age $\geq$ 50, CAD, hypertensive	Verapamil SR $\pm$ trandolapril (6391)	19/10 mmHg	All cause death, nonfatal MI or nonfatal stroke	0.98 (0.90–1.06)
			Atenolol $\pm$ HCTZ (6083)	19/10 mmHg		
VALUE, 2004 [27]	4.2	Age $\geq$ 50, high risk hypertensive	Amlodipine $\pm$ HCTZ (7649)	17/10 mmHg	Cardiac mortality and morbidity	1.04 (0.94–1.15)
			Valsartan $\pm$ HCTZ (7596)	15/8 mmHg		
ASCOT, 2005 [25]	5.5	Age 40–79, hypertensive plus 3 CV risk factors	Amlodipine $\pm$ perindopril (9639)	18/10 mmHg	Nonfatal MI and fatal CHD	0.90 (0.79–1.02)
			Atenolol $\pm$ bendroflumethiazide (9618)	15/10 mmHg		
ACCOMPLISH, 2008 [26]	3.0	Age $\geq$ 60, High Risk Hypertensive	Benazepril + amlodipine (5744)	14/7 mmHg	Death from CV causes, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after sudden cardiac arrest, and coronary revascularization.	0.80 (0.72–0.90)
			Benazepril + HCTZ (5762)	13/6 mmHg		

Combination Therapy Trials

Table 2
Randomized Clinical Trials and Observational Studies Reporting Incidence of New Onset Diabetes and Associated Cardiovascular Risk

Trial	Mean Years Follow Up	Primary Drug(s) (n w/out diabetes at entry)	Risk Ratio for NOD	BP Equivalency	Diabetes Definition (Prospectively Defined in RCT?)	CV Outcome Definition	Risk Ratio for CV Outcome in NOD Cohort
Trials with New Onset Diabetes Data Only							
CAPP [21]	6.1	Captopril (5138) β Blockers ± Diuretics (5230)	0.86 (0.74–0.99)	Yes	2× FPG ≥ 6.7 mmol/L (Yes)	N/A	N/A
STOP-2 [22]	4.0	ACEIs (1969) DHP CCBs (1965) β Blockers/Diuretics (1961)	0.96 (0.72–1.27) v BB/Diu 0.96 (0.74–1.31) v ACEI 0.97 (0.73–1.29) v CCB	Yes	2× FPG ≥ 6.7 mmol/L (Yes)	N/A	N/A
HOPE [60]	4.5	Ramipril (2837) Placebo (2883)	0.66 (0.51–0.85)	No	Patient Self-reported (No)	N/A	N/A
INSIGHT [17]	3.0	Nifedipine (2508) HCTZ+amloride (2511)	0.77 (0.62–0.96)	Yes	RPG > 11.0 mmol/L (Yes)	N/A	N/A
LIFE [19]	4.8	Losartan (4019) Atenolol (3979)	0.75 (0.63–0.88)	Yes	2× FPG ≥ 6.7 mmol/L (Yes)	N/A	N/A
NORDIL [18]	4.5	Diltiazem (5059) β Blockers/Diuretics (5095)	0.87 (0.73–1.04)	No	Not Specified (Yes)	N/A	N/A
ALPINE [102]	1.0	Candesartan ± felodipine (196) HCTZ ± Atenolol (196)	0.13 (0.02–0.99)	Yes	2× FPG ≥ 7 mmol/L, treatment, physician reported (Yes)	N/A	N/A
INVEST [24]	5.4	Verapamil ± Trandolapril (8098) Atenolol ± HCTZ (8078)	0.85 (0.76–0.95)	Yes	Physician diagnosed or patient reported (Yes)	N/A	N/A
PEACE [80]	4.8	Trandolapril (4140)	0.83 (0.72–0.96)	No	Not Specified (No)	N/A	N/A

Trial	Mean Years Follow Up	Primary Drug(s) (n w/out diabetes at entry)	Risk Ratio for NOD	BP Equivalency	Diabetes Definition (Prospectively Defined in RCT?)	CV Outcome Definition	Risk Ratio for CV Outcome in NOD Cohort
		Placebo (4116)					
ASCOT [25]	5.5	Amlodipine ± perindopril (7072) Atenolol ± bendroflumethiazide (7040)	0.70 (0.63–0.78)	No	FPG ≥ 7 mmol/L, physician reported (Yes)	N/A	N/A
COMET [101]	3.9	Carvedilol (1151) Metoprolol (1147)	0.76 (0.58 to 0.97)	No	2× RPG ≥ 11 mmol/L or Physician reported (Yes)	N/A	N/A
CHARM [81]	3.1	Candesartan (2718) Placebo (2721)	0.78 (0.64–0.96)	No	Physician reported (Yes)	N/A	N/A

Trial	Mean Years Follow Up	Primary Drug(s) (n w/out diabetes at entry)	Risk Ratio for NOD	BP Equivalency	Diabetes Definition (Prospectively Defined in RCT?)	CV Outcome Definition	Risk Ratio for CV Outcome in NOD Cohort
ALLHAT [114]	4.9	Chlorthalidone (9727)	0.80 (0.64–0.99)	No	FPG $\geq$ 7.0 mmol/L (No)	Mortality Combined CV Disease	1.31 (0.95–1.81) 1.04 (0.80–1.35)
		Amlodipine (5725) Lisinopril (5824)					
VALUE [115,118]	4.2	Valsartan (5032)	0.77 (0.69–0.87)	No	FPG $\geq$ 7.8 mmol/L, treatment, adverse event (Yes)	Cardiac Morbidity	1.43 (1.16 to 1.77)
		Amlodipine (4963)					
Samuelsson <i>et al</i> [108]	15	β Blockers or Diuretics or both (Observational)	N/A	N/A	FPG $\geq$ 7 mmol/L	CHD	1.48 (0.37–6.00)
Dunder <i>et al</i> [110]	17.4	Treatment (β Blockers or Diuretics or both)	N/A	No	Continuous BG measure	MI	1.37 (1.16–1.59)* 1.14 (0.98–1.32)*
		No Treatment					
Verdecchia <i>et al</i> [112]	6.0	Non-standardized Care (Observational)	Diuretic in 53.5% NOD vs 30.4% no-NOD, P=0.002	N/A	FPG $\geq$ 7 mmol/L or treatment	CV Disease	2.92 (1.33–6.41)
Amgren <i>et al</i> [107]	28	(Non-standard) β Blockers + Diuretics (725)	2.64 (1.41–4.94)**	N/A	FPG $\geq$ 7 mmol/L	Stroke	1.67 (1.10–2.56)
			0.61 (0.37–1.02)**			MI	1.66 (1.10–2.50)
						Mortality	1.42 (1.07–1.90)

* Hazard Ratios for effects of increase in blood glucose between age 50 and 60 for having an MI after age 60.

** Odds ratios for NOD following treatment with β blockers and with diuretics after 3 years.

FPG = fasting plasma glucose, RPG = random plasma glucose, BG = blood glucose, BB = beta blocker, HCTZ = hydrochlorothiazide, DHP = dihydropyridine, CCB = calcium channel blocker, CV = cardiovascular, CHD = coronary heart disease, MI = myocardial infarction, N/A = not available

Table 3

Mechanisms associated with metabolic effects of antihypertensive medications

RAS Blocking Agents (ACEIs and ARBs)	<p>Improved Insulin Sensitivity:</p> <p>Increased skeletal muscle perfusion</p> <p>Decreased hepatic glucose production (↓ Ang II)</p> <p>Enhanced adipocyte differentiation (↓ Ang II)</p> <p>Alterations of insulin signaling</p> <p>Change in proportions of oxidative muscle fibers</p> <hr/> <p>Improved Pancreatic β Cell Function:</p> <p>Increased pancreatic perfusion</p> <p>Increased serum potassium (improving K^+-ATPase function)</p> <p>Restoration of first phase insulin secretion (↓ Ang II)</p>
Thiazide Diuretics	<p>Diminished Insulin Sensitivity:</p> <p>Decreased skeletal muscle perfusion</p> <p>Increased hepatic glucose production (↑ Ang II)</p> <p>Inhibition of adipocyte differentiation (↑ Ang II)</p> <p>Increased endothelial inflammation</p> <p>Visceral and hepatic fat deposition</p> <hr/> <p>Diminished Pancreatic β Cell Function:</p> <p>Decreased pancreatic perfusion</p> <p>Decreased serum potassium (hindering K^+-ATPase function)</p> <p>Inhibition of first phase insulin secretion (↑ Ang II)</p>
β Blockers	<p>Reduced insulin secretion</p> <p>Reduced skeletal muscle perfusion</p> <p>Reduced pancreatic perfusion</p> <p>Weight gain</p> <p>Alteration of lipoprotein lipase activity</p>