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Intensive versus Standard Therapy for Hypertension: The Clinical Trials

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Abstract

Hypertension is a leading risk factor for premature death and disability. It can be controlled through lifestyle changes and use of antihypertensive medication. This review looks at intensive blood pressure reduction trials in non-diabetic, diabetic, and mixed patient populations. The primary hypothesis for the Systolic Blood Pressure Intervention Trial (SPRINT) is that treating to a systolic blood pressure target of < 120 mmHg (the intensive intervention) compared to a systolic blood pressure target of < 140 mmHg (the standard intervention) will reduce the primary composite outcome. Lowering systolic blood pressure more rigorously to 120 mmHg instead of the standard 140 mmHg can give substantial benefit according to the SPRINT. SPRINT showed efficacy in older patients above age 75 years. The ACCORD trials did not show efficacy for reducing primary outcomes with intensive therapy in a diabetic population with central obesity not being a significant factor. ACCORD found that intensive blood pressure reduction therapy benefited patients with atrial fibrillation, p-wave indices and left ventricular hypertrophy. Cerebrovascular protection was afforded diabetic subjects, but there was no additive advantage to tighter blood pressure control on microvascular outcomes. The 2014 Eighth Joint National Committee panel re-evaluated their own recommendation of relaxing initiation therapy for those over age 60 from systolic blood pressure of 140 mmHg to 150 mmHg with a post hoc analysis of INVEST (INternational VErapamil SR Trandolapril STudy) data that showed a more relaxed initiation standard would cause more harm to patients. The delicate balance of reducing cardiovascular morbidity and mortality with intensive blood pressure control while avoiding adverse events is an area of concern for clinicians. Many factors must be considered and the studies that address the intense versus standard therapy conundrum are discussed herein.

Introduction

High blood pressure affects over one billion people worldwide and is highly prevalent in the adult population of the US [1]. The importance of blood pressure as an independent risk factor for coronary events, stroke, heart failure, and progressive chronic kidney disease (CKD) including end-stage renal disease is well documented [2-12]. The Global Burden of Disease Study identified elevated blood pressure as the leading risk factor, among 67 factors studied, for worldwide mortality and disability-adjusted life years during 2010 [13]. Treatment of hypertension reduces cardiovascular disease outcomes, including incident stroke (35% to 40%), myocardial infarction (15% to 25%), and heart failure (up to 50%) as shown by numerous clinical trials [2,14,15]. The benefits of controlling blood pressure are clear and can be seen even with small reductions [16]. Treatment of hypertension is essential to reduce the high burden of cardiovascular disease, but unfortunately, there are many hypertensive persons worldwide who are not achieving adequate blood pressure control [17]. For the treating physician, target blood pressure is not always a distinct number and the threshold for treatment is controversial.

Advancing age brings an increasing prevalence of hypertension from about 7% in those age 18 to 39 years to 66% in persons above age 60 years, attributed to progressively higher systolic blood pressure (SBP) with age [18,19]. The need for multiple medications to bring down blood pressure in older persons can have unintended consequences. Among these are dizziness, orthostatic hypotension, falls and syncopal episodes [20,21]. Electrolyte imbalances such as hyponatremia and hypokalemia can occur, most notably with diuretics [22,23].

Despite gaps in knowledge, there is a wealth of information available and accumulating that addresses approaches to treating hypertension and blood pressure targets for varying demographic groups. This review looks at intensive blood pressure reduction trials in non-diabetic and diabetic patients to see the benefits of more intensive therapy on major cardiovascular events and secondary outcomes.

Trials in Subjects without Diabetes

The Systolic Blood Pressure Intervention Trial: SPRINT

Rationale and design

For the systolic blood pressure intervention trial (SPRINT), the primary hypothesis is that treating to a systolic blood pressure target of < 120 mmHg (the intensive intervention) compared to a systolic blood pressure target of < 140 mmHg (the standard intervention) will reduce the primary composite outcome of nonfatal myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and death from cardiovascular disease [24]. SPRINT, a 2-arm, multicenter, randomized clinical trial, enrolled large numbers of non-diabetic individuals age 50 and over with hypertension defined as baseline blood pressure average ≥ 130 mmHg systolic. Participants were enriched for cardiovascular disease and associated risk factors while those with history of prior stroke were excluded. The protocol recommended that anti-hypertensive regimens should include one or more drug classes with the strongest evidence for capacity to prevent cardiovascular disease outcomes: thiazide-type diuretics, calcium

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channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs), with priority for prescription of thiazide-type diuretics but discretion given to the physician to initiate and intensify therapy. Follow-up is scheduled to end in the fall of 2016.

Clinical outcome

After 1 year of the SPRINT trials the mean systolic blood pressure was 121.4 mmHg in the intensive-treatment group and 136.2 mmHg in the standard-treatment group. The intervention was stopped early owing to a significantly lower rate of the primary composite outcome and all-cause mortality in the intensive-treatment group compared to the standard-treatment group. However, rates of serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or failure, but not of injurious falls, were higher in the intensive-treatment group than in the standard-treatment group. The data suggests that lowering systolic blood pressure to 120 mmHg instead of to the standard 140 mmHg can be substantially beneficial in reducing the rate of primary outcomes and mortality with intensive treatment. However, it would be demanding, time-consuming, and would necessitate increased medication costs and clinic visits since only about 50% of the general population in the United States achieve current standard therapy systolic blood pressure levels [25].

Controlling Blood Pressure in the Older Patient: Sprint Substudy and Hyvet

The value of hypertension treatment in the elderly is an area of controversy and a variety of studies have suggested that the positive relationship between blood pressure and cardiovascular mortality is weakened or indeed reversed in the very elderly [26]. Older patients may have trouble handling more intense anti-hypertensive therapy because there may be detrimental effects [27]. One major concern is that blood pressure lowering may lead to dizziness and falls, especially in frail older persons. Falls are a major cause of morbidity and mortality in community-dwelling older adults and can diminish the quality of life by causing an increase in dependency and a limitation of activities of daily living.

SPRINT Substudy- Older non-diabetic patients

To address the question of whether benefits of intense lowering of blood pressure would be mitigated by dizziness, falls and other side effects of medications in older subjects, a SPRINT sub-analysis examined the issue. The substudy implemented a frailty index (FI) consisting of 37 items for participants of the SPRINT trial to see if older patients could handle intensive blood pressure control. The classification groups were fit (FI ≤ 0.10), less fit (0.10 < FI ≤ 0.21), or frail (FI > 0.21). When looking at 2510 SPRINT patients grouped by frailty status, the study showed that while patients with the highest degree of frailty had higher rates of heart disease and death, these rates were reduced with tighter blood pressure control in a way comparable to persons who were not considered frail. Among frail subjects, intensive blood pressure treatment did not significantly increase risk for injurious falls and other serious side effects. After a median follow up of 3.14 years, patients in intensive therapy had reduced primary outcomes and the overall rate of serious adverse events was not different between treatment groups suggesting patients over the age of 80 can see great benefits with intense antihypertensive therapy [28].

HYVET- Older non-diabetic and diabetic patients

The Hypertension in the Very Elderly Trial (HYVET) also examined the issue of medication regimens for control of hypertension in the elderly, but with a blood pressure target of 150/80. HYVET enrolled patients aged 80 years and older in a randomized, double-blind, placebo-controlled trial designed to assess the benefits of treating very elderly patients with hypertension comparing a low dose of the diuretic indapamide sustained release with the addition, if necessary to achieve target blood pressure, of the ACE inhibitor perindopril to placebo. Inclusion criteria included systolic blood pressure must be > 160 mmHg [29]. The target blood pressure for the experimental group was 150/80 mmHg. The patients in both arms were comparable to start with mean age of 83.6 years, mean blood pressure while sitting, 173.0/90.8 mmHg, and 11.8% had a history of cardiovascular disease. Data was collected over approximately 2 years of follow-up and benefits of treatment appeared after about 1 year. The mean blood pressure while sitting was 15.0/6.1 mmHg lower in the active-treatment group than in the placebo group. Treatment yielded reduction in rates for fatal or nonfatal stroke, death from any cause, death from cardiovascular causes, and heart failure with fewer serious adverse events suggesting the substantial benefit for treatment of patients above the age of 80 [30]. Total mortality decreased by 21% ($p = 0.02$) and cardiovascular events decreased by 34% ($p < 0.001$). Benefits appeared by the first year of follow up.

Table 1: Comparison between SPRINT and HYVET.

Column1	SPRINT	HYVET
Mean baseline age	67.9	83.6
Baseline seated BP	139.7/78.1	173.0/90.8
Target blood pressure	120/80	150/80
BP difference between experimental and control group	14.8/7.6	15.0/6.1
Primary outcome	Reduced events	Reduced events
Median frailty index	0.18	0.17
Medication	thiazide-type diuretics, calcium channel blockers (CCBs), angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs)	low dose diuretic (indapamide sustained release 1.5 mg daily) and additional ACE inhibitor (perindopril)
Physician discretion with prescription medication	yes	no

Comparing SPRINT and HYVET participants (Table 1) the median FI were similar at 0.18 and 0.17 for SPRINT and HYVET respectively. Similarly, the FI has been comparable to population studies with 2,570 (27.6%) of the SPRINT participants classified as frail. The data suggests that the inclusion of frail patients in large scale clinical trials assessing cardiovascular disease risk with aggressive blood pressure control such as SPRINT is appropriate [31].

Secondary Outcomes in Sprint

Chronic kidney disease

In designing SPRINT, the CKD sub population was scrutinized specifically due to their extraordinary risk for cardiovascular disease [32]. SPRINT data is available on kidney outcome, restricted to the CKD subgroup [16]. Among 9361 subjects randomized in SPRINT, 2646 (28.3%) had CKD at trial inception, defined as estimated glomerular filtration rate (eGFR) < 60 ml/min per 1.73 m^2 of body surface area. An additional 890 (9.5%) had baseline eGFR < 45 ml/min per 1.73 m^2. Those with eGFR < 20 ml/min per 1.73 m^2, 24-hour urine protein excretion ≥ 1 g/d or equivalent, or polycystic kidney disease were excluded. For participants with CKD at baseline, there was no significant difference between those randomized to the lower systolic pressure group and those in the standard systolic pressure group in the composite renal outcome of end-stage renal disease or a 50% decline in eGFR from baseline. There was also no difference in the development of incident albuminuria.

However, in patients without pre-existing CKD, a 3.5-fold higher incidence of a > 30% decrease in GFR was shown in the intensive group. Adverse events such as hypotension, syncope, hyponatremia, and acute kidney injury, were more frequent in those targeted to 120 mmHG. Overall, this leaves the clinician with hard choices in which optimal blood pressure for the cardiovascular system may not be ideal for the kidney [33].

African Americans have 2- to 4-fold greater likelihood of developing end stage renal disease than Americans of European

ancestry [34]. For reasons that are unclear, Apolipoprotein L1 gene (APOL1) G1 and G2 coding variants are strongly associated with CKD in African Americans [35]. Another substudy was conducted to determine *APOL1* G1 and G2 risk variant association with prevalent cardiovascular disease and baseline CKD, eGFR, and albuminuria in 2,571 African Americans SPRINT participants. SPRINT is well structured to examine the effects of systolic blood pressure targets on clinical outcomes as well as predictors influencing blood pressure control in African Americans [36]. The study looked at African Americans who had consented to take part in genetic studies within SPRINT with a mean age of 64.3 years, mean arterial pressure 100.7 mmHg, eGFR 76.3 ml/min per 1.73 m^2 urine albumin: creatinine ratio 49.9 mg/g, 8.2% had clinical cardiovascular disease defined as prior coronary or carotid artery revascularization (surgical or percutaneous) or myocardial infarction, and 45.3% were female. *APOL1* was positively associated with CKD and urine albumin: creatinine ratio, but negatively associated with eGFR. However, *APOL1* risk variants were not shown to be significant to cardiovascular disease, including myocardial infarction and coronary or carotid artery revascularization in this high-risk non-diabetic sample, suggesting *APOL1* risk variants are associated with mild CKD but not prevalent cardiovascular disease in African Americans [37].

Trials in Subjects with Diabetes

The Action to Control Cardiovascular Risk in Diabetes Trial: ACCORD

Rationale and design

Diabetes and hypertension are often found as comorbid conditions in patients. The combination of both hypertension and diabetes mellitus in an individual greatly increases the risk for cardiovascular events above the risk level for either condition alone [38]. Persons with diabetes have a substantially greater risk of cardiovascular-related mortality than non- diabetics at any given blood pressure [39]. The hypertension guidelines in 2004 from the US Department of Veterans Affairs and the US Department of Defense recommend a goal blood pressure in diabetes of < 140/80 mmHg [40]. Numerous clinical trials on hypertension with diabetes patients including Systolic Hypertension in the Elderly Program (SHEP) [41], Hypertension Optimal Treatment (HOT) study [42,43], United Kingdom Prospective Diabetes Study (UKPDS) [44,45], Systolic Hypertension in Europe (Syst-Eur) trial [46], and Appropriate Blood Pressure Control in Diabetes (ABCD) [46-48] trial have shown efficacy of hypertension reduction and reduced mortality outcomes. In a meta-analysis, the Blood Pressure Trialists' Collaboration [49] reported that the use of ACE inhibitors, calcium antagonists, ARBs, and diuretics or β-blockers in patients with and without diabetes reduced total major cardiovascular events to a comparable relative extent by regimens. There was limited evidence showing larger reductions in risk for major cardiovascular events with lower blood pressure goals in patients with diabetes than without diabetes. This latter finding provides support for conducting a more definitive test of the effect of intensive blood pressure-lowering in the setting of diabetes.

ACCORD examined the association between optimal glucose control (HbA1c < 6%) compared to conventional glucose control (targeted HbA1c 7-7.9%) and cardiovascular events. ACCORD was also designed to provide the first definitive clinical trial data on the possible benefit of treating to more aggressive blood pressure to a specific intensive therapeutic goal of < 120 mmHg with antihypertensive drug therapy compared to a strategy that targets a systolic blood pressure of < 140 mmHg in preventing cardiovascular disease in patients with diabetes where the primary outcome measure for the trial is the first occurrence of a major cardiovascular event, specifically nonfatal MI or stroke, or cardiovascular death with a follow up of 4-8 years [50]. Approximately 54% (4,733) of ACCORD participants were also part of the blood pressure arm of the trial. For the glucose control aspect of the study, there was an increase of 22% in mortality in the intensively treated group which caused investigators to stop the study in this arm after a mean follow-up period of 3.7 years.

Clinical outcome

Early results from multiple clinical trials have shown that reducing systolic blood pressure to < 140 mmHg results in 30%-60% reductions in cardiovascular events. More intensive therapy did not prove to reduce cardiovascular disease more effectively in diabetes [51]. A total of 4733 participants with type 2 diabetes were randomly assigned to intensive or standard therapy and the mean follow-up time was 4.7 years. The mean systolic and diastolic blood pressures of the participants at baseline were 139.2/76.0 mmHg. There was a larger reduction from baseline in the intensive therapy group compared to the standard therapy group with systolic blood pressure at 119.3 mmHg and 133.5 mmHg and diastolic blood pressure at 64.4 mmHg and 70.5 mmHg, respectively. The difference between the two therapy groups is associated with greater drug exposure in the intensive therapy group, 3.4 mean number of medications after the first year, compared to the standard therapy group, 2.1 mean number of medications after the first year. Rate of serious adverse events was significantly higher in the intensive-therapy group than in the standard-therapy group. 445 cardiovascular events occurred with 1.87% per year in the intensive-therapy group as compared with 2.09% per year in the standard-therapy group. This is not a significant difference between groups. Data suggests intensive blood pressure reduction therapy has no greater impact on reducing major cardiovascular outcomes in diabetic patients than the standard therapy [52].

Non-significant data between the two therapy groups could have varied based on level of central obesity amongst the participants. Sex-specific quartiles of waist-to-height ratio were used as the measure of central obesity for intensive and standard therapies. A ratio exceeding 0.60 was considered obese with women having a higher ratio than men. Results showed that baseline waist-to-height ratio did not significantly modify the risk of cardiovascular outcomes when comparing intensive and standard therapy groups, consistent with the main ACCORD study [53].

Combination Therapy for Hyperglycemia and Hypertension

A factorial study design in the ACCORD trial allowed analysis of combinations of standard and intensive treatment of glycemia with blood pressure. Although this was not the primary objective, unexpected results were generated [54-56]. Patients were randomized twice, first through varying HbA1c goals to study intensive versus standard glycemia treatment and second through systolic blood pressure for intensive versus standard blood pressure reduction therapy. For the blood pressure trial, the risk for cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke, was lower in the groups intensively treated for glycemia, blood pressure, or both when compared to the group receiving standard treatment for both glycemia and blood pressure which differs from the data in the primary ACCORD trials. However, the intensive combination therapy of blood pressure and glycemia treatment did not show significant benefit compared with either single intensive intervention [56].

Secondary Outcomes in Accord

Retinopathy

Retinopathy in diabetes is the most common microvascular cause of blindness in the United States [57]. Using the ACCORD and ACCORD Eye participants, a subset study used to evaluate certain medical strategies to understand the progression of diabetic retinopathy, the study looked at the use of intensive glycemic control, combination therapy for dyslipidemia, and intensive blood-pressure control to limit the progression of diabetic retinopathy in patients with type 2 diabetes compared to the current standard therapy. After a 4-year follow-up, when specifically isolating for intensive

blood pressure control therapy, the intensive therapy group showed a reduction in the progression of retinopathy over the standard therapy with 10.4% decrease and 8.8% decrease in progression rate, respectively. However, this data was not significant unlike intensive glycemia treatment and intensive dyslipidemia therapy [43].

Atrial fibrillation

Currently there are no proven strategies that prevent atrial fibrillation in type 2 diabetes, so a study was conducted to test whether intensive blood pressure reduction therapy was superior to standard blood pressure reduction therapy in decreasing the incidence of atrial fibrillation and p-wave indices using participants from the ACCORD trials. Data showed that the primary outcome incidence rates were 84.5 per 1,000 person-years in the standard-therapy group vs. 73.9 per 1,000 person-years in the intensive-therapy group, a greater reduction with strict control of blood pressure in type 2 diabetes patients that suggests potential benefit in preventing atrial fibrillation and p-wave indices [58].

Left ventricular hypertrophy (LVH)

LVH is a common complication of hypertension associated with cardiovascular morbidity and mortality [59-62] which has been shown to be reduced with regression of LVH [63-70]. Studies have shown that a reduction in blood pressure leads to regression of LVH [71] but does not show whether or not more intensive therapy than currently provided would lead to better outcomes. Using participants from the ACCORD trials, analysis revealed a 39% lower risk of LVH in the intensive therapy group compared to the standard therapy group after a median 4.4 years of follow-up. The risk reduction was attributed to the fact that the intensive group had a greater regression of the existing LVH as well as a decrease in incidence of new LVH. Data suggests favorable effects of intensive blood pressure lowering on LVH and reduction of cardiac mortality in patients with type 2 diabetes and increased cardiovascular risk [72].

Cardiovascular outcomes in CKD with diabetes

Patients with CKD are at high risk for developing cardiovascular disease, but highly vulnerable to adverse effects of prescribed medication, suggesting alternative methods should be studied. One study assessed the impact of intensive antihypertensive therapy on the cerebrovascular and other cardiovascular outcomes in high-risk patients with type 2 diabetes and baseline CKD using participants of the ACCORD trials. In the intensive therapy group, patients without CKD and with CKD had a 55% significant reduction and 38% reduction in the rate of any stroke, respectively. Data suggests intensive anti-hypertensive therapy provides significant cerebrovascular protection for patients without CKD, however significant therapeutic benefits for patients with CKD, though not proven in this study, cannot be excluded [73].

Microvascular complications

Blood pressure lowering has been shown to reduce microvascular complications in patients with type 2 diabetes mellitus [30,31,74]. Data from the ACCORD trial was analyzed to see whether intensive anti-hypertensive therapy could lead to a further reduction in microvascular complications, using 10 predefined outcomes. These outcomes included development of renal failure, nephropathy, retinopathy and neuropathy. After a follow up of a median 4.7 years, the data showed that microvascular complications occurred in 11.4% of intensive and 10.9% of standard blood pressure control patients. Thus, there was no significant association between intensive control of blood pressure and improved microvascular outcomes. The study also showed no interaction between intensive glycemic control and intensive blood pressure control. This suggests that there is no incremental benefit provided by intensive anti-hypertensive therapy on microvascular outcomes in diabetes [75].

Medication Regimens

Thiazides

Yet another substudy stemming from SPRINT looked into the patterns of prescription for thiazides, first line agents for hypertension [76,77]. Thiazides are commonly used therapy for elevated blood pressure. They are low in cost, well-tolerated and have been used with efficacy for over 40 years [78]. A cross sectional analysis revealed that at baseline, 43% of SPRINT patients were receiving thiazide treatment, but among those receiving monotherapy for hypertension, only 16% were prescribed a thiazide over other anti-hypertensive agents such as ACE inhibitors, β-blockers, or dihydropyridine calcium channel blockers. Thiazide administration was skewed toward younger subjects those with better renal function and African Americans.

Prescribing practices for thiazides vary based on multiple factors, but they may be under prescribed in general. In an observational study of treatment for resistant hypertension in the U.S., less than 60% of visits recorded thiazide use, despite the recommendation for their use in this condition [79,80].

Clinicians tend to avoid prescribing thiazides and thiazide-like (chlorthalidone and indapamide) diuretics to older patients even though HYVET showed fewer adverse events in the active treatment group compared to placebo. Other clinical trials such as the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT) and the NatriliX SR versus CandEsartan and amLodipine in the reduction of systoLic blood prEssure in hyperteNsive patienTs study (X-CELLENT) support use of thiazide and thiazide-like diuretics as a first line hypertensive treatment in older subjects [81,82].

In clinical practice there may be fears of increased adverse effects which is supported by some data. Thiazides have been shown to induce hyponatremia, especially in elderly persons with low body mass index or low sodium diet [83]. Greater risk of decreased serum sodium with thiazides occurs if there are comorbidities such as heart failure, CKD or malignancy [84,85].

A cross sectional analysis of SPRINT subjects showed that women were more likely than men to receive thiazide diuretic treatment [24]. A number of older studies from the 1990s also show a tendency to treat more women than men with thiazides and more recent studies continue this pattern [86-88]. Reasons for using this class of medication in women include the positive effect on calcium handling with reduced osteoporotic fracture risk and the avoidance of ankle swelling that can occur with CCBs [89].

Angiotensin II Converting-Enzyme (ACE) Inhibitors and Angiotensin II Receptor Blockers (ARBs)

ACE inhibitors and ARBs are first line treatments for patients with diabetes mellitus and hypertension [90]. These drugs show nephroprotective and cardioprotective properties as well as blood pressure optimization [91-93] reducing the risk of cardiovascular-related events and mortality [90]. However, prescribing practices for patients with diabetes varies significantly. A study by Rosen, et al. made use of a subset of data from subjects with diabetes age 55 and older who participated in the National Health and Nutrition Examination Survey and found national estimates of ACE inhibitor/ARB use in the elderly diabetic population to be 43% overall and a maximum of 53% in subjects with diabetes and 4 other clinical indications. This result is exceedingly low since the data suggested that almost all of the patients should be treated [94]. This is based on the recommendation that diabetes occurring with select additional risk factors (hypertension, albuminuria, cardiovascular disease) should be treated with ACE inhibitors or ARBs. Another study included adults diagnosed with diabetes mellitus from the National Ambulatory Medical Care Survey (NAMCS) during 2007-2010. They found patients with comorbidities such as hypertension, hyperlipidemia, and ischemic heart disease were more likely to be prescribed ACE inhibitors or ARBs. However, even though 64.1% of the study population had hypertension with diabetes mellitus, only 37.9% of these patients received a prescription for an ACE inhibitor/ARB [95].

In The United Kingdom Prospective Diabetes Study (UKPDS), diabetic subjects were randomly assigned to tight or less tight blood pressure control over a 4-year period. Tight control included an ACE or beta-blocker and looser control did not. Tight control was

associated with reduction of risk of death and other diabetes related endpoints. However, once the study ended, post-trial follow-up showed that differences in blood pressure between the 2 groups were lost and so were the benefits of the previous tight control. There was no legacy effect [96]. The issue of the legacy effect remains uncertain and it has been suggested that the initial 4 years was too short to confer an enduring advantage after discontinuation of tight control [97]. Overall, the evidence favors ongoing control of blood pressure, preferably starting early, as the best approach.

Both ACE inhibitors and ARBs block angiotensin II, an effector protein of the renin-angiotensin system, which can induce bone loss. Therefore, the use of these drugs may reduce bone loss and fractures. One study compared the incidence of fractures in older hypertensive men using ACE inhibitors or ARBs with CCBs. The study looked at approximately 6,000 men older then the age of 65 with a baseline bone density measured through the Osteoporotic Fractures in Men Study. After mean follow-up of 6.8 years, ACE inhibitors and ARBs each showed a significantly lower fracture incidence than non-users with the hazard ratio of non-vertebral fractures three times lower in ARB users than ACE inhibitor users. The research suggests superiority for ARBs in conferring a lower incidence of fractures. However, there was a trend of greater fracture risk reduction with longer duration of ARB use, but not for ACE inhibitor use [98].

In a study of drug efficacy, 24-hour ambulatory blood pressure responses were compared over 12 weeks in 304 subjects with stage 1 or 2 hypertension given 4 weeks of the ARB valsartan 160 mg, followed by 4 weeks of valsartan 320 mg and finally valsartan 320 mg combined with hydrochlorothiazide 12.5 mg. Response to valsartan monotherapy was poorer in patients older than 65 years (10% of subjects in this study) and in black patients (34% of subjects in this study). However, regardless of age or race, adding low dose hydrochlorothiazide with valsartan proved to be more efficacious than titration of an ARB when adjusting medication [99].

In African Americans, there is data from the ALLHAT study suggesting that systolic blood pressure was lower with diuretic treatment than with ACE inhibitor treatment (difference of 4 mmHg after 5 years of follow-up). Hispanic participants achieved good control with common medications, including thiazide-type diuretics. The data from the SPRINT participants suggests intervention in clinical settings for prescribing practices to match current guidelines and data to create better global outcome [100].

Beta blockers

An important aspect of medication to consider is the effect of the drug or drugs on a patient's quality of life, including sexual function. Several studies have shown associations of sexual dysfunction with male use of β-blockers and diuretics but it is unclear whether anti-hypertensive drugs are associated with female sexual dysfunction [101]. Using a cross sectional evaluation of the associations among different classes of antihypertensive medications and (a) sexual activity and (b) sexual function among female participants 50 years and older at high risk for cardiovascular disease, analysis showed no significant differences in sexual activity among women taking one or more antihypertensive medications and women not taking any. However, data did suggest that women take ACEI or ARB had increased odds of sexual activity. Although no class of medication were significantly associated with sexual dysfunction, 52% of sexually active women were below the cutoff for sexual dysfunction [102].

INVEST (INternational VErapamil SR Trandolapril STudy) [103]

Rationale and design

While SPRINT and ACCORD trials looked at more intensive anti-hypertensive therapy, the 2014 Eighth Joint National Committee (JNC-8) panel sought to evaluate threshold blood pressure for initiation of therapy in patients age 60 and over. The panel initially recommended that therapy be started when systolic blood pressure was < 140 mmHg. However, their recently published paper loosened the therapeutic target to < 150 mmHg for patients 60 years of age and over [104]. Due to the confusion and controversy surrounding the initiation of therapy, the JNC-8 sought to test their most recent recommendations. They wanted to determine an optimal cutoff systolic blood pressure at which to begin treatment. They therefore performed a post-hoc analysis using data from patients enrolled in the INternational VErapamil SR Trandolapril Study (INVEST).

INVEST contained 22,576 patients 50 years of age or older with hypertension that required drug treatment and coexisting coronary artery disease randomized to a multidrug anti-hypertensive strategy of either the calcium antagonist verapamil-SR or the β-blocker atenolol (non-calcium antagonist). Specifically, for the study of systolic blood pressure, 8,354 patients ≥ 60 years of age with baseline SBP of ≥ 150 mmHg were chosen. Trandolapril and hydrochlorothiazide were added if needed for blood pressure control to achieve blood pressure goals of < 140 mmHg (systolic) and < 90 mmHg (diastolic); and < 130 mmHg (systolic) and < 85 mmHg (diastolic) if diabetes or renal impairment was present. Patients were categorized into three groups: group 1, < 140 mmHg; group 2, 140 to < 150 mmHg; and group 3, ≥ 150 mmHg. Primary outcome was first occurrence of death (all-cause), nonfatal myocardial infarction, or nonfatal stroke while secondary outcomes were all-cause mortality (all-cause), cardiovascular mortality, total myocardial infarction (fatal and nonfatal), nonfatal myocardial infarction, total stroke (fatal and nonfatal), nonfatal stroke, heart failure, and revascularization.

Clinical outcome

Out of the total 8,354 patients included in the study 57% achieved systolic BP of < 140 mmHg, 21% achieved systolic BP of 140 to < 150 mmHg, and 22% achieved systolic BP of ≥ 150 mmHg with group 1 having the lowest rates of the primary outcome, all-cause mortality, cardiovascular mortality, myocardial infarction, total stroke, and nonfatal stroke without any increase in adverse experiences (Table 2). This data contraindicates recently published findings which suggested that lower blood pressure may not be better [105-108]. The data suggests that patients ≥ 60 years of age with coronary artery disease who fail to achieve an on-treatment systolic blood pressure of < 140 mmHg have a significantly increased risk of stroke and other adverse outcomes. It is important to note that this study was not designed to measure whether or not even lower systolic blood pressure is superior unlike the SPRINT and ACCORD trials. The American Heart Association and American College of Cardiology maintain a systolic blood pressure goal of < 140 mmHg in those over age 60.

Conclusion

High blood pressure affects nearly 80 million adults in the US and the prevalence is expected to expand over the next 15 years [109]. Due to its asymptomatic nature it can frequently remain

Table 2: INVEST study results.

Coloumn 1	Group 1 (< 140 mmHg)	Group 2 (140 to < 150 mmHg)	Group 3 (≥ 150 mmHg)
% achieved target SBP	57%	21%	22%
Primary outcome	9.36%	12.71%	21.32%
All-cause mortality	7.92%	10.07%	16.81%
Cardiovascular mortality	3.26%	4.58%	7.80%
Myocardial infarction	1.07%	1.03%	2.91%
Total stroke	1.19%	2.63%	2.91%
Non-fatal stroke	0.86%	1.89%	2.86%

Table 3: Comparison among SPRINT, ACCORD, and INVEST.

Coloumn 1	SPRINT	ACCORD	INVEST
Cardiovascular and mortality benefits	Significant	Non-significant	Most beneficial in group 1
Participants	Non-diabetic	Diabetic	Coronary artery disease
Sample size	9361	4733	8354
Mean cohort age	67.9	62	70.7
Study objective	Intensive antihypertension therapy	Intensive antihypertension therapy	Efficacy of relaxed initiation therapy SBP
Baseline BP	139.7/78.1	139.2/76.0	165.4/90.2

undiagnosed and untreated. Hypertension is a major risk factor for cardiovascular disease, and, with lifestyle changes and medications, it is modifiable. The number and combination of drugs available to manage hypertension is large and this has both negative and positive implications. Clinicians and patients have many choices, but the range of possibilities makes treatment complex and the potential for side effects may lead to under-treatment or non-compliance. To add to the problem, there is a lack of consensus on treatment targets, especially in older persons and those with diabetes. This review has presented results of some landmark trials that have attempted to resolve questions concerning goals for optimal control of blood pressure (Table 3). The answers are still indistinct and there will undoubtedly be future studies to bring more clarity to the subject. At this time, the information available can be synthesized by the treating physician as a multi-pronged, personalized action plan designed to obtain blood pressure control with the least possible number of well-tolerated medications.

The results of the Sprint Trial in particular have raised questions regarding the appropriateness of the JNC 8 recommendations [104], but we believe it is premature to commit all patients to the lower targets suggested by the SPRINT results. There are several reasons for this. The first is that the benefit in the intensive target cohort was driven primarily by a reduction in the development of heart failure, which is consistent with most other studies examining the effect of anti-hypertensive treatment. But this is in the context of the SPRINT results not demonstrating a reduction in stroke, which is at significant variance from virtually all other findings of blood pressure lowering trials. Reduction in stroke incidence was found in ACCORD. As such, it raises important questions about the lower target, because the explanation of this discrepancy would require a novel mechanistic description of how the antihypertensive regimens work. Because of the consistent finding of reduced stroke incidence across antihypertensive trials, the type of antihypertensive drug regimen does not appear to explain the reduction, so differences in the drug regimens does not explain this unusual finding in the SPRINT trial. Another puzzling finding is the reduction in all-cause mortality, which is encouraging, but without a plausible explanation prevents the SPRINT results from necessarily directing a change in guidelines. Lastly, the SPRINT population included a significant majority of patients who were already treated with anti-hypertensive agents before enrollment, and therefore cannot necessarily be considered in the high-normal range, and this therefore tempers the recommendations that therapy should be initiated even if the SBP is below 140 mmHg. Given these concerns, we suggest that all high cardiovascular risk patients be treated to a blood pressure of < 140/90 mmHg, and refer the reader to the various guidelines presently available for additional direction [104,110]. We await further trial data to refine our understanding of this important risk factor, so that practitioners can better customize therapy for their patients.

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