Treating Hypertension Near the Eighth Decade of Life:

Benefit or Burden?

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Dedication

My scholarly project is dedicated to my family who supported me throughout my graduate education. Their continuous inspiration made this composition worthwhile. I am very blessed and grateful for their endless love.

"Keep your dreams alive. Understand to achieve anything requires faith and belief in yourself, vision, hard work, determination, and dedication. Remember all things are possible for those who believe." – Gail Devers

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"Dedication is not what others expect of you, it is what you can give to others." – Unknown

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Introduction

"If you or someone you know suffers from high blood pressure ask your doctor about a medicine that is right for you." These words are repeated over and over on television in an attempt to reach the 27% of people in the United States who suffer from high blood pressure (U.S. Department of Health and Human Services Centers for Disease Control and Prevention, 2001-2004). According to a recent National Hospital Ambulatory Medical Care Survey, there are approximately 38 million visits per year to healthcare offices for the treatment of hypertension (Centers for Disease Control and Prevention, 2007). Unfortunately, only 25% of those with hypertensive readings have controlled blood pressure (Hyman & Pavlik, 2001). The World Health Organization (WHO) claims 4.5% of diseased people both developed and non-developed countries can attribute their illness to hypertension, and estimates that 7.1 million mortality cases around the world are due to hypertension (World Health Organization, 2003). Hypertension affects various age ranges; however, as medicine advances and our geriatric population grows, the need for proper healthcare in the aged is becoming a fundamental concern. Data from the CDC indicates that 67.1% of males and 82% of women above the age of 75 and have hypertension. It is estimated by the year 2030, 1 in every 5 Americans (20% of the population) will be over 65. This statistic emphasizes the needs to understand the management of hypertension in this population (Centers for Disease Control and Prevention, 2007).

A shortage of current, definitive evidence makes the treatment of hypertension difficult in this population and may explain the reluctance of some providers to treat it (Beard et al., 1992). A study conducted in Finland surveyed people who were at least 75 years old and had been prescribed cardiovascular medications. This study showed an increase in medication prescription from 1998-2003. The researchers realized an apparent need for re-evaluation after

treatment to determine the effectiveness of the cardiovascular medications (Hitola, Enlund, Sulkava, & Hartikainen, 2007). Most of the current trials have inclusion criteria beginning at 50-60 years of age but exclude several older participants due to underlying co-morbidities. There are many healthy elderly people nearing their 80's, and a solid consensus is needed as to whether treatment would benefit these patients. The lack of current studies pertaining to the older population and certain drug therapies is well known. We already know the benefits of treating hypertension in the general population. The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has published seven reports and will be publishing the eighth in the near future. These reports are filled with guidelines for the treatment of hypertension (Chobanian et al., 2003).

The likelihood of cardiovascular disease continuing to be the number one cause of death and disability remains very high. If blood pressure goes uncontrolled for even a short period of time, the patient is still at a substantial risk for future sequelae. This is especially true in older patients (Lloyd-Jones et al., 2005). The purpose of this clinical review is to break down various trials utilizing aging patients with either isolated systolic hypertension (ISH) or generalized hypertensive blood pressure readings. A closer look was also taken at head-to-head trials comparing characteristics of several medications and their overall effects. After evaluating these trials, recommendations will be made regarding the management of hypertension in the very elderly. (The definition of very elderly will be patients nearing their eightieth year of life and also including patients above 80 years old.) In general, the ultimate goal of antihypertensive therapy is to decrease morbidity and mortality in these patients while improving their overall well-being and functional ability.

Background

Who exactly is at risk for developing hypertension? New evidence has shown that people in their 5th decade of life are at a 90% continuing risk of becoming hypertensive in their lifetime (Vasan et al., 2002). Elevated blood pressure values are a solid contributor to atherosclerotic cardiovascular disease and the most significant influence on stroke (Goldman & Ausiello, 2004). One of the most problematic issues is the lack of definitive limit for a blood pressure reading in relationship to morbidity and mortality. Hypertension is often asymptomatic until late in its course, and by this point the damaging effects of this condition have already begun. Approximately 95% of high blood pressure readings are categorized as idiopathic (Kumar, Ramzi, & Robbins, 2003). A decrease in blood pressure reduces morbidity and mortality related to ischemic heart disease (IHD), heart failure, and stroke. Furthermore, the opportunity for complications is directly proportional to advancing age (Kumar et al., 2003).

There are two main components to the regulation of blood pressure: cardiac output and total peripheral resistance. Several other factors contribute to the hemodynamics of blood pressure including genetic factors, environment, and demographics. Angiotensin II and catecholamines regulate vasoconstrictive properties. The vasodilatory responses are controlled by kinins, prostaglandins, and nitric oxide. The combined effects of the vasoconstrictors and dilators influence blood pressure inside the body. When the blood volume and peripheral resistance become too high, arterial hypertension will be the end result. The pliability of the conduit vessels declines with age. Hypertensive states exacerbate this process which then leads to an increasing amount of atherosclerotic plaques. The vasculature undergoes morphological changes which involve hyaline thickening and stenosis of the lumen walls. This narrowing of the arteries is almost inevitable in the very aged. The thickening is mostly due to fatty

composites and calcium salts which adhere to the walls of the artery result in a narrowed lumen for blood flow (Weller & Wiley, 1985). As the endothelium begins to lose elasticity, fibrous connective tissue and smooth muscle take over to decrease overall vessel compliance (Weller & Wiley, 1985). This change often occurs in predictable and generalized locations. The calcified walls cause a decrease in compliance resulting in an increase in afterload. As the heart is forced to work harder to pump the blood through the vessels, a rise in left ventricular mass is a common result.

Advancing age imposes an increased risk for hypertension. The increased risk contributes to overall morbidity and mortality in those elderly affected by hypertension. Vascular decline, erectile dysfunction, nephropathy, and retinopathy are all sequelae of hypertension. These conditions are not only commonly found in the elderly, but also can significantly impact quality of life. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure developed standards to manage hypertensive patients at a target reading below 140/90 mm Hg. Systolic readings above the guidelines are a better predictor of future cardiovascular complications when compared to a high diastolic value (Chobanian et al., 2003). Unfortunately, isolated systolic hypertension is seen most commonly in older adults who are already at the most risk for a cardiovascular event. The reason for this offset is actually well understood and follows a basic principle of hemodynamics. Diastolic values augment with sustained peripheral arterial stricture and then reversibly decrease with the calcification of larger main arteries, which tends to happen in older age (Wang et al., 2005). The calcification in the large conduit arteries directly contributes to isolated systolic hypertension. Research examining isolated systolic hypertension, diastolic hypertension, and combined hypertension must be evaluated carefully and thoroughly in the elderly.

Controversy remains on how far systolic blood pressure can be lowered without harming the patient by lowering a normal diastolic pressure too far. An investigation used patients from the first phase of the Systolic Hypertension in Europe Trial to examine this controversy (Fagard et al., 2007). An association was formulated utilizing the Cox regression analysis. Placebo and active group data was used to ensure adequate results. The study consisted of 4,695 randomized patients: 2,225 in the placebo group and 2,358 in the active treatment group. The average age of all participants was 70.2 years. Approximately 46% of the patients had been on antihypertensive treatment 6 months prior to the study (Fagard et al., 2007). About 30% of the participants had a cardiovascular history. A substantial decrease in diastolic pressure was not found to be significantly related to cardiovascular mortality. A maximum diastolic blood pressure lowering of no more than 55 mm Hg from baseline is recommended in most patients. A diastolic pressure of 70 mm Hg diastolic pressure is reasonable for known heart disease patients (Fagard et al., 2007). Therefore, this study supported aggressive treatment of ISH when necessary.

Isolated Systolic Hypertension Trials

Final Results of the Systolic Hypertension in the Elderly Program (SHEP)

The SHEP trial was a randomized, double-blind, placebo controlled trial, performed over several years. This trial was the first completed trial studying isolated systolic hypertension (Perry Jr et al., 2000). The researchers focused on treating isolated systolic hypertension and the effect on stroke. Secondarily, an assessment of cardiovascular relationship was included. The events studied were the following: sudden cardiac death, severe cardiac symptoms without a defined cause, non-fatal and fatal myocardial infarction, left ventricular failure, other cardiovascular death, transient ischemic attack, coronary artery bypass graft or coronary angioplasty, and renal dysfunction (S. C. R. Group, 1991). The recruitment process maintained a balance between the active and placebo groups in regards to race, sex, previous medical history, and other related variables. A total of 4,736 participants above the age of 60 were involved in the study. The average age of all the participants was 72 years. There were 1,061 patients in the 70-79 age range in the active treatment group and 1,059 in the placebo group. In the 80 years old and beyond, 331 participants were involved in active treatment and 317 in the placebo groups (S. C. R. Group, 1991).

Sixty-six percent of the participants were not currently on antihypertensive medication. Fewer than 2% had a stroke history, and fewer than 6% had a history of myocardial infarction. Systolic blood pressure above 160 mm Hg and diastolic below 90 mm Hg were trial prerequisites. These values were averaged from four readings on two separate occasions. Blood pressure goal was less than 160 mm Hg if the participant's blood pressure was higher than 180 mm Hg at baseline. Blood pressure goal when a participant was above 160 mm Hg but below 179 mm Hg was a systolic decrease of 20 mm Hg (S. C. R. Group, 1991).

Treatment began with low doses of one medication. Researchers attempted to maintain adequate blood pressure control with a stepwise approach, taking into consideration that elderly participants may already be on several medications. For this reason, researchers chose to seek a simplified antihypertensive regimen. The first step medication was 12.5 mg daily of chlorthalidone, a thiazide-type diuretic (S. C. R. Group, 1991). Chobanian (et al., 2003) stated in the most recent JNC Seven Report that first line therapy for treatment of hypertension should include a thiazide-type diuretic. The committee recommends diuretics because of their low cost and effective amplification of antihypertensive therapy. The report declared diuretics are not used enough in current medical practice. In the SHEP trial, if blood pressure was not controlled with the 12.5 mg of chlorthalidone, the dose was increased to 25 mg daily. An additional 25 mg daily of atenolol was added if hypertension was still uncontrolled after increasing the diuretic dose. If patients were unable to tolerate atenolol, then reserpine was substituted at 0.5 mg daily. A group of study participants required 50 mg of atenolol to reach target blood pressure. (See Figure 1.) Potassium levels were monitored and supplements were given if needed to avoid hypokalemia related to diuretic use (S. C. R. Group, 1991).

The active treatment group showed a 26 mm Hg decrease in systolic pressure readings after 3 months when compared to initial values. A decrease in 9 mm Hg diastolic pressure was observed in the active group. The placebo group produced a 15 mm Hg decrease in systolic readings from original values. A decrease in 5 mm Hg was obtained in diastolic pressure from original data. The goals set at the beginning of the study were met by approximately 68.5% of the active treatment participants and 36% of placebo members (S. C. R. Group, 1991).

As mentioned earlier, stroke was the main focus of the study and cardiovascular criteria examination followed. The active group suffered l54 fewer strokes over four and a half years of

examination. Stroke events were lower in the active versus placebo group in all age brackets. Data closest to the eighth decade of life were the 70-79 year old participants with 48 versus 74 placebo stroke events. In the 80 and above age group, 21 versus 38 placebo stroke events occurred. Analyzing the 70 and above participants, a total of 43 fewer stroke events were seen when comparing the active versus placebo groups. Regression analysis produced a p-value of 0.0003 making these comparisons statistically significant. A concern was noted in the active treatment group with serum electrolyte values being out of the recommended ranges. The SHEP trial did not report the percentage of values, which were not in the desired ranges. It is important to follow lab values and additional attention should be given to potassium, uric acid, glucose, cholesterol, and sodium to maintain normal levels during treatment with thiazide diurectics (S. C. R. Group, 1991).

In conclusion, the SHEP trial provides valuable evidence to support treatment of ISH in patients 60 years and beyond. Overall, a 36% decrease in stroke was seen over the course of data collection (S. C. R. Group, 1991). An investigation following the SHEP trial found a decrease in both ischemic and hemorrhagic strokes (Perry Jr et al., 2000). The most significant data showed a benefit in antihypertensive therapy and a decrease in ischemic strokes. Eighty-five ischemic strokes were observed in the chlorthalidone group compared to 132 ischemic strokes in the placebo group. A lower occurrence of lacunar and other unspecified subcategories of stroke were also found (Perry Jr et al., 2000). Similar data was found in the atherosclerotic strokes in active versus placebo groups. Atherosclerotic stroke was determined by carotid duplex or angiogram. A minimum of 70% stenosis of the diseased artery was the diagnostic criteria of an atherosclerotic stroke in this study.

Researchers also found participants in the active treatment group who suffered a stroke experienced less overall disability from the stroke. Individuals in the treatment group spent less time in the hospital and were able to be active before the placebo group. The p-value was significant for this comparison at 0.03. It is impossible to prevent all strokes with treatment alone; however, this study proves treatment may accelerate post-stroke recovery. Finally, a 32% decrease was observed in the active versus placebo group for all cardiovascular related events (Perry Jr et al., 2000).

Starting treatment with the stepwise approach may be particularly successful in the elderly. A thiazide-type diuretic is a great first line drug for treating hypertension (Chobanian et al., 2003). This trial succeeded in proving the highest percentage of blood pressure control could be maintained using the lowest dose treatment regimen. Chlorthalidone at 12.5 mg daily controlled 30% of hypertensive participants (S. C. R. Group, 1991).

Improving quality of life is an important goal of antihypertensive therapy. This may be even more important for our very elderly receiving treatment. In the past, clinicians have been concerned that antihypertensive therapy could have undesirable effects on cognitive health, such as mood and depression. An evaluation throughout the SHEP study was completed to determine a relationship between treatment and its effect on mood, daily life, and other generalized activities on all study participants (Applegate, 1998). A baseline evaluation was performed before treatment began and biannual follow up for cognitive related concerns. More specific evaluations of cognitive ability and basic lifestyle questions enhanced the overall evaluation. Contrary to prediction, treatment did not cause a negative influence on cognition. The study was divided into three variables. The variables monitored were basic, moderate, and advanced activities of daily function (Applegate, 1998). The active treatment performed better on all three

evaluation variables when compared to the placebo group. A p-value of 0.05 was formulated from data indicating significant mood deterioration in the non-treatment participants. Active treatment participants remained more active and less affected by the disease. Treatment of ISH will improve functional ability in the majority of patients 60 years and beyond who are diagnosed with ISH (Applegate, 1998).

Pittsburg SHEP Cohort Investigation

Paralleling the SHEP trial was the Pittsburg SHEP Cohort Investigation. This investigation focused on antihypertensive treatment and its relationship to cardiovascular health. An additional evaluation of atherosclerosis also enhanced the study. A control group of 187 people with normal blood pressure were added to the evaluation of 135 active treatment participants and 133 placebo participants to create an estimate of cardiovascular relationships. Participants were all above 60 years old and the average age in all groups was 73.5 years old. Prerequisites for the study were systolic blood pressures above 160 mm Hg and below 219 mm Hg for the Pittsburg SHEP group. The control group participants had blood pressure readings below 160 mm Hg. All three groups had diastolic readings below 90 mm Hg. Treatment was replicated from the SHEP trial described earlier (Sutton-Tyrell, Wildman, Newman, & Kuller, 2003).

An evaluation for baseline atherosclerosis was completed on all participants. The screenings confirmed clinical atherosclerosis, subclinical atherosclerosis, or lack of evidence to support atherosclerosis. An examination of atherosclerotic free individuals showed a smaller amount of cardiovascular related events in the active and control groups after comparison to the placebo group. The researchers confirmed a correlation between cardiovascular outcome and presence of atherosclerosis; however, participants with disease taking antihypertensive

medication showed a delay to cardiovascular related events (Sutton-Tyrell et al., 2003). Data showed the most benefit of treatment to be around four years of therapy. The Kaplan-Meier approach to statistical analysis was used to compute a 14 year estimate obtained from trial data. This analysis places placebo, active, and control groups from highest to lowest in relation to cardiovascular event rates. The approximate percentages were 46%, 26%, and 21% respectively (Sutton-Tyrell et al., 2003).

After completion of this study researchers found a 90% chance of a cardiovascular related event for non-treated individuals with ISH over 14 years. If treatment is initiated early in stages of ISH there is a more favorable prognosis. Positive outcomes of early treatment include decreased stiffening of the conduit arteries, less systolic hypertension, and fewer CV related events (Sutton-Tyrell et al., 2003).

Trial of Older Chinese patients with ISH (Syst-China)

The Syst-China trial is another study focused on isolated systolic hypertension in the elderly. The mean age in this study of 66.5 years is lower than the majority of the trials examined for hypertension in the elderly. The goal of the trial was to examine antihypertensive treatment and the effect on stroke, cardiovascular events, and all-cause mortality (Lisheng, Wang, Gong, Liu, & Staessen, 1998). An average of three years was spent following up the 2,394 people enrolled in the trial. The mean blood pressure was 170.5 mm Hg systolic and 86 mHg diastolic. A total of 1,253 patients were on the active treatment group and 1,141 were on the placebo group. All patients were initially started on placebo treatment; then groups were divided into treatment and placebo groups. The researchers took important characteristics into consideration such as sex and prior cardiac history when dividing the two groups. A stepwise approach was used for implementing the medication. Initially nitrendipine (calcium channel

anatgonist) at 10-40 mg daily was used. An additional 12.5-50.0 mg of captopril (angiotensin converting enzyme │(ACE)│inhibitor) or hydrochlorothiazide (diuretic) was added in attempt to lower pressure (Lisheng et al., 1998). Both additional drugs were needed to maintain target blood pressure in some individuals. Blood pressure goal was a decrease of 20 mm Hg or a drop below 150 mm Hg (Lisheng et al., 1998).

Results for this study were fairly consistent with the other major ISH studies in the United States. A decrease of 38% in total stroke incidence produced a statistically significant p-value of 0.01. An overall lowering of all-cause mortality by 39% estimated a significant p-value of 0.003. Cardiovascular mortality and stroke mortality were decreased by 39% and 58% with coinciding statistically significant p-values of 0.03 and 0.02. This study found that treatment was preventative against stroke and other cardiovascular co-morbidities in older patients with ISH (Lisheng et al., 1998).

The Syst-Eur Trial

The Systolic Hypertension in Europe (Syst-Eur) trial examined the effects of antihypertensive therapy and cardiovascular results in the aged (Staessen, Thijs, Gasowski, Cells, & Fagard, 1998). This double blind placebo controlled study contained participants who were at least 60 years old. Mean age of all participants was 70.2 years old. Enrollment took place in various European countries. A total of 4,695 participants were recruited and randomly assigned to different treatment regimens. Nitrendipine at 10-40 mg daily was the first step of treatment. Enalapril (ACE-inhibitor) at 5-20 mg daily and hydrochlorothiazide 12.5-25 mg daily were added in certain cases to achieve adequate blood pressure readings. When patients were randomized, blood pressures spanned from 173.8 ± 10 mm Hg systolic and 85.5 ± 5.9 mm Hg diastolic. Average sitting blood pressure upon entry was 173.8/85.5 mm Hg. Both treatment

groups were randomized into two groups: 2,398 on antihypertensive therapy and 2,297 on placebo treatment. Approximately 5% of the examinees had a history of stroke or myocardial infarction (Staessen et al., 1998).

The researchers obtained enough data to support a significant conclusion after the second interim analysis. After approximately two years of follow up, the trial was halted in February of 1997 (Staessen et al., 1998). Total stroke occurrence decreased by 42% in the treatment group. This finding had a very significant p-value of 0.003. Cardiovascular related activity endpoints were also reduced significantly by 31%. Death attributed to cardiovascular causes declined; however, this value was not statistically significant (Staessen et al., 1998).

A subgroup analysis was an additional side examination of the Syst-Eur trial. Data obtained from the Syst-Eur trial was formulated into an equation in an attempt to see if treating hypertension lost benefit after a certain age. A Cox regression breakdown for treatment-by-age produced a predicted increase in cardiovascular mortality; however, the results were not statistically significant. The Syst-Eur researchers determined that advantages of treatment may be lost in patients beyond 75 years old. A similar estimate also showed that participants with smaller systolic readings at the start of the trial had a better outcome in regards to total mortality (Staessen et al., 1998).

Meta-analysis of Outcome Trials

A cluster of clinical trials examining systolic hypertension over the past few decades have included elderly patients. A group of researchers chose to combine data from eight trials and compute a meta-analysis to estimate overall outcome (Staessen et al., 2000). The trials limited to isolated systolic hypertension patients were SHEP, Syst-Eur, and Syst-China. The trials also limited to ISH with a subgroup of elderly patients were European Working Party on

High Blood Pressure in the Elderly Trial (EWPHE), Systolic Hypertension in Elderly Program (SHEP), Swedish Trial in Old Patients with Hypertension Trial (STOP), Medical Research Council Trial of treatment of hypertension in older adults (MRC1), and MRC2. Most of these trials were previously mentioned or will be mentioned in this clinical review. Non-parametric style and Cox regression were the primary techniques used to evaluate total trial data. Many variables were evaluated during this analysis including lone mortality, cardiovascular mortality, cardiovascular related events, and stroke. A total of 15,693 participants were involved in the trials and followed for an average of 3.8 years. All trial participants were greater than or equal to 60 years old, with an average age around 70. Medical history revealed 4,848 with previous cardiac concerns, 217 with a past stroke, and 357 with a previous MI. The mean systolic pressure of all participants was 174 mm Hg, and the mean diastolic was 83 mm Hg (Staessen et al., 2000).

A concentrated examination of the three ISH trials showed a statistically significant ($p = 0.008$) 17% decrease in overall mortality (Staessen et al., 2000). A 25% decrease was seen in cardiovascular related deaths. A 37% drop in stroke rate and a decrease in coronary activity by 25% were also significant. Data from the eight trials showed an enhanced benefit of treatment for men, aged persons 70 and beyond, and people with a positive cardiovascular history. A change in 10 mm Hg systolic pressure reading can significantly affect a patient's overall risk. There is an independent correlation raising the overall risk by 10% if the reading increases by 10 mm Hg (Staessen et al., 2000). Researchers concluded that treatment of elderly hypertensive patients should be guided and most influenced by systolic values. Systolic pressures above 160 mm Hg warrant therapy, and research shows this group has the highest benefit of reducing stroke

occurrence. More information is necessary to evaluate precise effect of antihypertensive therapy and coronary relationship (Staessen et al., 2000).

Critique of the ISH trials

The five studies previously mentioned pertained to isolated systolic hypertension in the aged. Due to a high proportion of the elderly who have ISH, these studies are very important in addressing that specific population. Researchers realized the need for such specific data. Other than the Pittsburg-Cohort trial, all of the ISH trials had a sufficient number of participants to reach a reliable conclusion. The lowest number was 2,394 participants in the Syst-China study, and the highest was 4,736 in the SHEP trial. The elderly benefit from a slow stepwise treatment process, and the following four trials made an extra effort to follow this approach: SHEP, Pitt-SHEP, Syst-China, and Syst-Eur. The Syst-China trial paid more attention to the elderly with ISH and diabetes mellitus, straying somewhat from the "fit" elderly as a target research group. The majority of participants in all of these trials were in their early 70's. Further studies with a threshold age of 70 would provide additional useful information in the management of the very elderly with ISH.

Combined Systolic and Diastolic Hypertension

Total Mortality in the Swedish Trial in Old Patients with Hypertension Trial

The Swedish Trial in Old Patients with Hypertension (Stop-Hypertension) patients was performed in Sweden in 1991. This double-blinded randomized placebo trial included 1,627 males and females with ages ranging from 70 to 84 years old. The qualifications for this study were systolic blood pressure values ranging from 180-230 mm Hg and diastolic pressure of 90 mm Hg or above, also including a sole elevated diastolic pressure greater than 105 mm Hg but less than 120 mm Hg (Dahlof et al., 1991). The participants were not being actively treated when obtaining baseline values. All patients in the study had not experienced a myocardial infarction or stroke in the past 12 months. The focus of this study was to examine the effect of treatment on cardiovascular disease, fatal and nonfatal myocardial infarctions, as well as both types of stroke (Dahlof et al., 1991). Various individual beta-blockers as well as a combination of a beta blocker and diuretic were chosen for treatment. These drugs were the most common forms of antihypertensive treatment in Sweden at the time of the trial (Dahlof et al., 1991).

Dahlof et.al (1991) uncovered valuable information pertaining to the geriatric population. They found that treating elderly patients up to the age of 84 years old significantly lowered blood pressure readings when compared to the placebo group. An overall decrease was also seen in primary endpoints, including stroke, myocardial infarction, and cardiovascular related death (Dahlof et al., 1991). A statistically significant decrease was seen in all primary endpoints in the antihypertensive treatment groups. A decrease of 36 primary endpoints in the treatment group created a p-value of 0.0031. A drop in stroke morbidity and mortality was also discovered with 24 fewer events and a p-value of 0.0081. A decrease in total mortality was also observed when comparing the treatment and placebo groups. The corresponding p-value for total mortality was

0.0079 with 27 fewer deaths. Overall, this trial concluded that there is benefit to treating hypertensive patients into the early eighth decade of life if the patient maintains blood pressure values used in this study (Dahlof et al., 1991).

Medical Research Council Trial

This MRC Working Party focused on general outcome due to treatment of hypertension in older adults. The MRC Working party created a randomized-single blind placebo study to evaluate antihypertensive treatment and related outcomes to stroke, coronary heart disease, and total mortality (Peart et al., 1992). Treatment was initiated with diuretics, beta-blockers, or placebo. A total of 4,396 patients between the ages 65-74 years old with qualifying blood pressure readings were included in the study. The blood pressure readings were taken over an eight week period and averaged to obtain a baseline value. Entry criteria were a systolic reading between 160-209 mm Hg and a diastolic less than 115 mm Hg. Atenolol was the beta-blocker of choice at 50 mg daily. The alternate treatment group consisted of 25 mg of hydrochlorothiazide plus 2.5 mg of amiloride. The third group was a placebo treatment. Target systolic blood pressures were set from 150-160 mm Hg in respect to baseline reading. Blood pressures were followed for 12 weeks, and treatment was enhanced when necessary if pressures were not adequately controlled. Atenolol was raised to 100 mg daily in 5% of the trial participants. In special cases, additional drugs were still needed to reach blood pressure goals. Nifedipine at 20 mg daily was randomly assigned to these special cases (Peart et al., 1992).

In the first quarter of the trial all treatment groups displayed a reduction in blood pressure. Both treatment groups had blood pressure readings reduced more than the placebo group. The diuretic group saw the most significant decrease in blood pressure readings. A two year follow-up revealed similar systolic and diastolic blood pressure readings in both treatment

groups. The placebo group maintained the highest systolic and diastolic blood pressure readings throughout the data collection. Unfortunately, this trial suffered a large amount of attrition due to complications. The diuretic group declined by 160 participants with several complaints of impaired glucose tolerance. Several adverse effects also caused a decline in the beta-blocker group by 333 participants. Many of these participants experienced Raynaud's phenomenon. Eighty-two placebo participants left due to adverse effects, and 175 were lost from insufficient management. Altogether, 25% of the participants were not included in re-evaluation (Peart et al., 1992).

The diuretic group showed the most significant effect on stroke, coronary cases, and overall mortality. A p-value of 0.03 was produced from a significant decrease seen in cardiovascular related events. The beta-blocker group failed to show a significant influence on the studied events. Total mortality due to any cause was similar in treatment and placebo groups. This trial supports treatment of elderly hypertension with a combination of diuretics to reduce cardiovascular related events (Peart et al., 1992).

The European Working Party

The European Working Party on High Blood Pressure took a closer look at treatment versus placebo in relation to morbidity and mortality results. The multicenter trial began in 1972 and ended earlier than anticipated in 1984. Data showed initial trial endpoint goals had been achieved. This trial was randomized and double-blinded, controlled by placebo. All participants were above the age of 60 with an average age of all participants was 72 years. Entry blood pressure was between 160-239 mm Hg systolic and 90-119 mm Hg diastolic. Average blood pressure of all participants was 183/101 mm Hg. Exclusion criteria included congestive heart

failure, history of cerebral or subarachnoid hemorrhage, hepatitis, cirrhosis, and malignancy (Amery et al., 1985).

All participants were split into treatment or placebo groups. A total of 840 people were in the final data, 416 active treatment and 424 placebo patients. The treatment group was given 25 mg of hydrochlorothiazide and 50 mg triamterene (antikaliuretic). After 14 days, both dosages could be doubled if necessary. Furthermore, if blood pressure was still uncontrolled, an additional 500 mg of methyldopa could be given to the participants in a stepwise fashion. Half doses progressing up to four tablets daily was the treatment protocol. About 35% of the active treatment group required methyldopa tablets (Amery et al., 1985).

The Mantel-Cox estimate was the statistical analysis used by the researchers. An insignificant reduction of all types of mortality was estimated from the data. A decrease in cardiac mortality and total cardiovascular mortality was significant. The correlating p-values were as follows: cardiac mortality $p=0.036$ and cardiovascular mortality $p=0.037$. Interestingly, a minute decrease in cerebrovascular mortality created a non-significant p-value of 0.15. A decrease in cerebrovascular events was seen that was not statistically significant (Amery et al., 1985).

INDANA Meta-analysis

The antihypertensive drugs in very old people: a subgroup meta-analysis of randomized controlled trials was done by the INDANA group. This analysis pulled data from older patients out of a group of published trials. It consisted of a review of the following five trials with participants over 80 years old: European Working Party on High Blood Pressure in the Elderly (EWPHE), Systolic Hypertension in the Elderly Program pilot (SHEP-P), SHEP, and STOP-H. The majority of these trials have been mentioned or will be mentioned later in this review. The

primary outcome examined was the effect of antihypertensive therapy on stroke (Gueyffier et al., 1999).

The data proved to be fairly consistent with the trials examined after breaking down the age groups. Treatment of hypertension in patients over 80 years old showed a drop in 34% in stroke incidence. The correlating p-value with the data evaluated was 0.014 and statistically significant. A benefit was also seen in regards to decreased incidence of cardiovascular events and heart failure; however, the p-value was not statistically significant. This review of trials showed a benefit to decrease stroke incidence as well as a small percentage of reduction in cardiovascular related events and heart failure. The researchers stated a special designed trial was needed to reinforce their conclusion, and this may have prompted the formation of the next trial reviewed (Gueyffier et al., 1999).

HYVET Pilot Trial

The pilot study for the Hypertension in the Very Elderly Trial (HYVET) was an open study trial from 1994-1998. These researchers felt there was a lack of clear evidence to support treating hypertension in the elderly and wanted to remedy this (Bulpitt et al., 2003). The participant qualifications were at least 80 years old with a regular blood pressure between 160-219 mm Hg systolic and 90-109 mm Hg diastolic. The mean age of the participants was 83.8. Mean systolic blood pressure upon entry was 181.5 systolic and 99.6 diastolic. One thousand two hundred and eighty-three participants were divided evenly and at random to receive either thiazide diuretic (bendrofluthiazide), ACE inhibitor (lisinopril), or placebo. The dosages of medications are as follows: bendrofluthiazide 2.5 mg, lisinopril 2.5 mg, diltiazem (calcium channel blocker) slow release at 120 and 240 mg. The diltiazem was added if the diuretic and/or ACE-inhibitor had been doubled. If necessary, diltiazem was included in treatment regimens to

maintain adequate blood pressure. The trial noted all generic names were not exactly the same. The names mentioned above were the most common; however, this trial required only specific drug classes across the various treatment trial centers. Patients included in this trial were fairly healthy elderly. Serum creatinine levels above 150 μmol/l and severe congestive heart failure were two of the major exclusion criteria. Stroke in the past six months was also exclusion criteria. About 3% of the patients had a history of myocardial infarction and 4.5% had a history of stroke. The average BMI of all participants was 25 kg/m^2 (Bulpitt et al., 2003).

Blood pressures decreased similarly in both treatment groups. The diuretic group averaged a drop by 26/15 mm Hg. The ACE-inhibitor group averaged a decrease by 27/16 mm Hg. A slight decrease was noted in the placebo group with a 3/4 mm Hg change. Although reduction in stroke events and stroke mortality were seen with the treatment groups, total mortality was increased in the treatment groups. Therefore, the question of whether treatment is beneficial could not be answered by this trial (Bulpitt et al., 2003).

HYVET Trial

Following the pilot study, the randomized, double-blind placebo-controlled HYVET trial examined the effects of treating hypertension in 3,845 patients 80 years of age or older. The average age of all participants was 83.6 years old. This made HYVET a landmark study because the majority of previous trials contained patients in their early 70's and did not have a significant number of patients in their 80's. One thousand nine hundred and thirty-three patients were placed in the active treatment group, and 1,912 were placed in the placebo group. Various exclusion criteria were utilized in order to obtain a "fit" elderly population in the study. A few examples of the exclusion criteria were an occurrence of a hemorrhagic stroke in the past six months, congestive heart failure requiring pharmacotherapy, and secondary hypertension

(Beckett et al., 2008). Creatinine and potassium levels were required to fall within a certain range to be enrolled in the study. All participants had a minimum systolic pressure of 160 mm Hg upon entry. Several variables were studied; however, fatal and nonfatal stroke were the primary endpoints. Secondary endpoints were designated as all-cause mortality, cardiovascular mortality, and stroke mortality. Approximately 11.8% of the participants had a history of cardiovascular disease (Beckett et al., 2008).

The first line anti-hypertensive treatment was 1.5 mg of indapamide sustained release (SR). Indapamide is structurally similar to a diuretic. If further treatment was needed then 2-4 mg of perindopril was given in order to reach target blood pressure. Blood pressure goal was set at 150/80 mm Hg. If additional medications were needed for an extended period of time, these patients were excluded from follow-up. The median follow-up on participants after start of the study was 1.8 years. A decrease was seen of 15 mm Hg in systolic blood pressure and a decrease of 6.1 mm Hg in diastolic blood pressure in the active treatment group (Beckett et al., 2008).

At two year follow up, almost 20% of the placebo patients had reached the goal blood pressure, and almost 50% of the active treatment group had also reached goal. In the active treatment group 25.8% of the patients were treated only with indapamide. Twenty-three point nine percent of the patients were receiving indapamide plus 2 mg of perindopril. Lastly, the majority,49.5%, were receiving indapamide plus 4 mg of perindopril. A decrease in 30% was seen in stroke incidence creating a p-value of 0.06. The rate of death caused by stroke was decreased by 39% creating a statistically significant p-value of 0.05. A 21% decrease was seen in all cause mortality with a statistically significant correlating p-value of 0.02. Mortality related to a cardiovascular cause decreased by 23% with a p-value of 0.06. Significant data was seen with a reduction in heart failure by 64%. The reduction in heart failure included fatal and non-

fatal types. The p-value for reduction in heart failure was statistically significant with $p<0.001$. A decrease of 34% was seen with multiple cardiovascular events creating a statistically significant p-value of $p<0.001$. The criteria included were cardiovascular causes, stroke, myocardial infarction, or heart failure. In previous trials, researchers had become moderately concerned with potassium values after treatment with thiazide diuretics; however, at the two year follow up there was not a significant difference seen in the potassium values of patients from pre-therapy to post-therapy data (Beckett et al., 2008).

The data obtained from the HYVET trial is similar to the results obtained from the HYVET pilot study as well as the Individual Data Analysis of Antihypertensive Drug Intervention Trials (INDANA) group meta-analysis. The study showed that treating patients for hypertension with systolic readings greater than or equal to 160 mm Hg was beneficial. The suggested treatment is indapamide with additional peridonpril if needed to reach goal blood pressure. By following these guidelines, the patients' risk of mortality will be significantly lowered (Beckett et al., 2008).

Critique of Combined Systolic and Diastolic Hypertension

The five trials mentioned above focused on various ranges of hypertension. For the most part, these trials had a significant number of participants to ensure accurate data. The STOP-H trial had an impressive follow-up percentage of 100%. Trials often lose people to follow-up which may skew their concluding data; however, the STOP-H trial was able to report complete data. The European Working Party trial spanned several years, which enables one to obtain more accurate results. Most importantly for this clinical review, the HYVET-pilot trial as well as the HYVET main trial had participants 80 years old and beyond. As mentioned earlier with the ISH trials, it would have been beneficial for these studies to have a higher age threshold for

trial participants. The HYVET-pilot trial did follow through with the elderly criteria; however, it is difficult to make a solid conclusion on one study. Following the pilot trial was the main HYVET trial which showed a significant benefit to antihypertensive therapy into the eighth decade of life. The publication of the HYVET trial was a major breakthrough because the majority of the previous trials are outdated. The need for this fresh new research is high due to our healthy aging population and advances in health care.

Head to Head Trials

If hypertension is to be treated in the elderly, which drug to use becomes a question. A few major head-to-head trials of antihypertensive drugs that included elderly participants were examined to address this question. Head to head trials comparing characteristics of various medications are also beneficial in obtaining data for overall effects on morbidity and mortality. A randomized study examined the effects of old and new antihypertensive medications on cardiovascular morbidity and mortality in older patients (Hansson et al., 1999). A total of 6,614 study participants between the ages of 70-84 years old were involved. Inclusive blood pressure readings were greater than/equal to 180 mm Hg systolic and greater than/equal to 105 mm Hg diastolic. The "older" drugs used in the study were hydrochlorothiazide or various beta-blockers: atenolol, metoprolol, and pindolol. The "newer" medications used were the following: enalapril, lisinopril, felodipine, or isradapine. The participants were divided randomly into either conventional, ACE inhibitor, or calcium antagonist groups. The primary objective of this study was to compare fatalities related to stroke, MI, and cardiovascular disease in the groups (Hansson et al., 1999).

The data showed a similar decrease in all three treatment groups of approximately 34.6/16.7 mm Hg. Various pieces of information can be pulled from this study. Cardiovascular

mortality and morbidity impediment was about the same in all three groups (Hansson et al., 1999). The breakdown of endpoints in each group is as follows: 460 "old" medications, 437 ACE-inhibitor, 450 calcium antagonists. A relative risk was calculated for group to group comparison, and none of the results were statistically significant. There was no major difference between the various drugs in regards to stroke prevention. After concluding this study, the researchers advocate a basic approach to treating hypertension in the elderly. A medication should be chosen based on cost, adverse effects, and relationship to additional health disease to accommodate each patient and his or her varying needs. Furthermore, a cross-examination comparing this trial and the STOP-Hypertension trial, which was mentioned earlier, showed ACE-inhibitors provide added protection for all myocardial infarctions when compared to calcium channel blockers. This comparison also showed a smaller percentage of patients who were taking an ACE-inhibitor with congestive heart failure when compared to a calcium channel blocker (Hansson et al., 1999).

Another study found that ACE-inhibitors are superior to thiazide diuretics (Wing et al., 2003). The study was randomized and open-labeled. Approximately 6,083 participants were enrolled between the ages of 65 to 84 years old. The enrolled patients were fit and active elderly with an unimpressive cardiovascular history. Follow-up of participants was 4.1 years. Entry criteria for the study required a minimum systolic blood pressure of 160 mm Hg or minimum diastolic blood pressure of 90 mm Hg. Patients and data were managed at his or her primary care practice office. The overall goal was systolic lowering by 20 mm Hg or less than 160 mm Hg. If feasible, a further lowering to 140 mm Hg was advocated. A diastolic lowering of 10 mm Hg or less than 90 mm Hg was the first goal. Again, if permissible a diastolic lowering less than 80 mm Hg was suggested. The main objective being studied was related to total cardiovascular

events or death attributed to all cause (Wing et al., 2003). A special effort was made to keep the participant groups similar in regards to physical characteristics. At conclusion of the study, 65% of the diuretic patients and 67% of the ACE-inhibitor patients were only on the designated drug. Around 5% of both groups were receiving three more medications. The remaining participants fell in between the monotherapy and polytherapy participants (Wing et al., 2003).

Similar reductions in blood pressure were found in both medications throughout the entire study. At the end of the first year, blood pressure decreased 20 mm Hg systolic and 9 mm Hg diastolic in the ACE-inhibitor group. Systolic blood pressure decreased 22 mm Hg and 9 mm Hg diastolic in the diuretic group. Toward the end of the study, data remained similar for both groups. There was no difference in first coronary events when comparing diuretics to ACE-inhibitors (Wing et al., 2003). On the contrary, fewer first time myocardial infarctions were observed in the patients who received ACE-inhibitors ($p=0.04$). Approximately 14% fewer non-fatal cardiovascular events were seen in the ACE-inhibitor group with a significant p-value of 0.03. Furthermore, a drop by 32% in first nonfatal heart attacks with a p-value of 0.05 was also seen in the ACE-inhibitor group. In regards to mortality and cardiovascular/noncardiovascular events, there was no significant difference noted between the two treatments. There was a statistically significant decrease in stroke mortality in the ACE-inhibitor group. The correlating p-value was 0.04. The researchers analyzed the data between male and female subjects and found the differences in treatment groups to be most prominent with males. This evidence demonstrates an added benefit to treating elderly males with an ACE-inhibitor (Wing et al., 2003).

The ALLHAT trial compared an ACE-inhibitor and calcium channel blocker to a diuretic. The researchers wanted to know which drug would be the best first line therapy for

someone diagnosed with a new onset hypertension after age of 55 (T. A. o. a. C. f. t. A. C. R. Group, 2002). A total of 33, 357 participants aged 55 and older were enrolled in this study. All participants had hypertension and at least one other coronary heart disease risk factor. The medications and dosages included in the study were the following: chlorthalidone (diuretic) 12.5 to 25 mg, amlodipine (calcium channel blocker) 2.5 to 10 mg, and lisinopril (ACE-inhibitor) 10 to 40 mg. The average age in all treatment groups was 66.9 years old. Approximately 8,784 participants in the chlorthalidone group, 5205 in the amlodipine group, and 5,185 in the lisinopril group were above the age of 65. The average blood pressure at the baseline reading in all three groups was 146/84 mm Hg. The participants were followed up for an average of 4.9 years (T. A. o. a. C. f. t. A. C. R. Group, 2002).

The main focus of the study was on mortality and coronary heart disease, or nonfatal myocardial infarctions (T. A. o. a. C. f. t. A. C. R. Group, 2002). A subset of focused events in the study were all-contribute mortality, stroke, combined coronary heart disease and cardiovascular disease. The data was broken down into comparing amlodipine and lisinopril individually to the chosen diuretic, chlorthalidone. The first drugs to be compared were amlodipine and chlorthalidone. Participants of the amlodipine treatment group showed a significant increase by 38% of heart failure ($p<0.001$). A higher risk of hospitalization or fatal heart failure was also noted in this group ($p<0.001$). Next, lisinopril was compared to the chlorthalidone treatment group. There was no significant difference when examining the main focus of the study between the two groups. Participants in the lisinopril group had a 15% increase in stroke incidence (p-value=0.02). There was also a 10% increase in risk for combined cardiovascular disease (p-value < .001). The average systolic blood pressure reading at follow-up was higher in the lisinopril group by two mm Hg(T. A. o. a. C. f. t. A. C. R. Group, 2002).

African American patients were noted to respond differently. There were 10,702 African American participants spread throughout the three treatment groups. The African American patients treated with lisinopril had a systolic reading of 4 mm Hg higher than all other participants. Data showed a varying effect of race when treating African Americans with lisinopril for stroke and combined cardiovascular disease. A poor blood pressure benefit was seen when using ACE inhibitors in black patients. Reports also showed a decreased ability of lisinopril to prevent heart failure in African American patients. The approximate p-values for drug and race relationship were 0.01 and 0.04 (T. A. o. a. C. f. t. A. C. R. Group, 2002).

Overall, researchers for the ALLHAT group promote chlorthalidone for first line antihypertensive therapy when compared to amlodipine or lisinopril. This treatment choice proved to be most beneficial all across all groups. Chlorthalidone also proves to be the most economical choice when discussing pharmaceutical drug costs. Thiazide diuretics have shown to be the most effective in lowering blood pressure and decreasing morbidity, have fewer side effects, and are less expensive when compared to competing antihypertensive medications (T. A. o. a. C. f. t. A. C. R. Group, 2002).

Thiazide Diuretics and the Risk for Hip Fracture

As previously mentioned, the ALLHAT research group found thiazide-type diuretics to be an optimal first line treatment choice. Other researchers have examined the association between length of thiazide treatment and risk for hip fracture (Schoofs et al., 2003). The initial thought behind this study was provoked by the idea that thiazides decrease urinary elimination of calcium. Thiazide diuretics increase calcium reabsorption and protect against bone loss caused by aging. The pre-study hypothesis was that the bone sparing effect of thiazide diuretics would decrease the incidence of fractures. The study consisted of 7,891 people over the age of 55 in the Netherlands. Various types of thiazide diuretics were used such as: plain thiazides, potassium sparing, and chlorthalidone. Chlorthalidone is not a formal thiazide; however, it has the same result for calcium excretion so it was treated as such (Schoofs et al., 2003).

Data was divided in increments according to the duration of thiazide treatment: never treated with medication, 1-42 days, current use for 43-365 days, current use for over 1 year, stoppage of use from one to 60 days, stoppage of use from 61 to 120 days, and stoppage of use for more than 120 days (Schoofs et al., 2003). There was an inverse association between duration of thiazide use for more than a year and fractures. The adjusted hip fracture risk declined to 0.46 (Schoofs et al., 2003). Raw data showed that participants over the age 80 had the most benefit from thiazide treatment. There was not a significant difference between the older group and the younger groups. Overall, researchers concluded that using thiazide diuretics continuously for over a year can decrease risk of hip fracture. A smaller period of time shows improvement; however, statistics were not significant until at least a year of therapy. Furthermore, if treatment is stopped, the preservative effect of the medication is lost after four months. This study enrolled more women; therefore, results may be more applicable to elderly

females (Schoofs et al., 2003). Because this study did not have similar numbers of male and female participants, it cannot be definitively stated that elderly males will reap the same benefits of thiazide diuretics in preventing hip fractures.

Conclusion

The question of whether to treat hypertension in the very elderly is not a new concern. A burst of studies were conducted in the mid 1980's and into the 1990's. After the large SHEP trial, there was not another major trial for several years. The HYVET trial, which was published May 2008, is the next biggest gain in research. The HYVET trial did not contain nearly as many people as the SHEP trial did; however, it included patients who were 80 and beyond. With medical technology and healthcare advances, it would not be shocking if the baby boomer generation further increased predicted lifespan. Some patients can be controlled with monotherapy; however, combination therapy is probably more realistic when considering the average patient with accompanying co-morbidities. The HYVET study provided a skeleton for further research. A study conducted with patients at least 70 years old, not excluding patients with co-morbidities, and comparing combination therapy would be helpful in the future. Some patients are now being managed by a two-medication pill combination, and that may prove to be another area for new study. The new combination medications may eventually be less costly and easier for the older patients by decreasing their daily pill count. However, as the research shows, a diuretic is a great first line therapy. Another route must be taken if a patient's blood pressure is still not controlled using a diuretic. The new combination medications joining diuretics and angiotensin receptor antagonists, beta-blockers, and calcium channel blockers should be studied in the future.

The first major question is whether treating hypertension in the elderly is beneficial or harmful. The older studies were not able to give a definite answer to that question. Hence, the majority of the studies showed a benefit for antihypertensive therapy, most notably a reduction in stroke. A few studies showed a possible correlation between antihypertensive therapy and an

increase in overall mortality. The recently published HYVET trial disproved this hypothesis and supported that antihypertensive therapy can continue into the eighth decade of life without concern for increased mortality.

Several of the trials examined used a thiazide diuretic for first line antihypertensive therapy. These trials also showed a significant benefit of stroke and cardiovascular related event reduction. All pharmaceutical therapy comes with risks or side effects. In general, thiazide diuretics are fairly safe; however, patients must be followed carefully to avoid complications that can be caused by the medication. Due to its mechanism of action, various electrolyte abnormalities can occur. Thiazide diuretics inhibit the sodium and chloride carriers in the distal tubule of the kidney to block reabsorption. The efficacy of therapy is regulated by the concentration of the medication within the tubular lumen.

In order to avoid the risk of unnecessary complications these elderly patients must be monitored closely. Adverse outcomes attributed to thiazide diuretics are hypokalemia, significant decrease of extracellular fluid volume, hyponatremia, hypomagnesemia, metabolic alkalosis, and hyperuricemia. Thiazide diuretics are also calcium sparing which may become a complication in hyperparathyroid patients. On the positive side, as mentioned earlier, thiazide diuretics may be therapeutic in osteopenic and osteoporotic patients with hypertension. Thiazides are beneficial by reducing urinary calcium excretion and avoiding bone loss in patients with hypercalciuria. Data previously mentioned showed a decrease in hip fracture risk. This was especially true in older females affected by bone density loss.

The SHEP, STOP-H, HYVET pilot, and HYVET trials were the most contributory to this clinical review due to the higher average age of participants. The primary end point studied was stroke. Generally stating, these trials found a significant decrease in stroke reduction utilizing a

stepwise approach to therapy. First line treatment was most commonly a thiazide diuretic and therapy advanced when needed using an ACE-inhibitor, beta-blocker, or less commonly a calcium channel blocker. Other factors must be considered when choosing baseline as well as additional therapy. Alternating co-morbities, such as systolic or diastolic dysfunction may change therapy choices completely. Also, patients on several medications may not be able to tolerate this general approach to antihypertensive therapy. It must restated that this review was targeting the "fit" elderly with fewer co-morbidities in which a thiazide diuretic would be appropriate first line therapy. Additional therapy should then be titrated to the patient's medical history and current medications for adequate management. As the population ages, future research should continue to guide our evidence-based management of hypertension in the very elderly.

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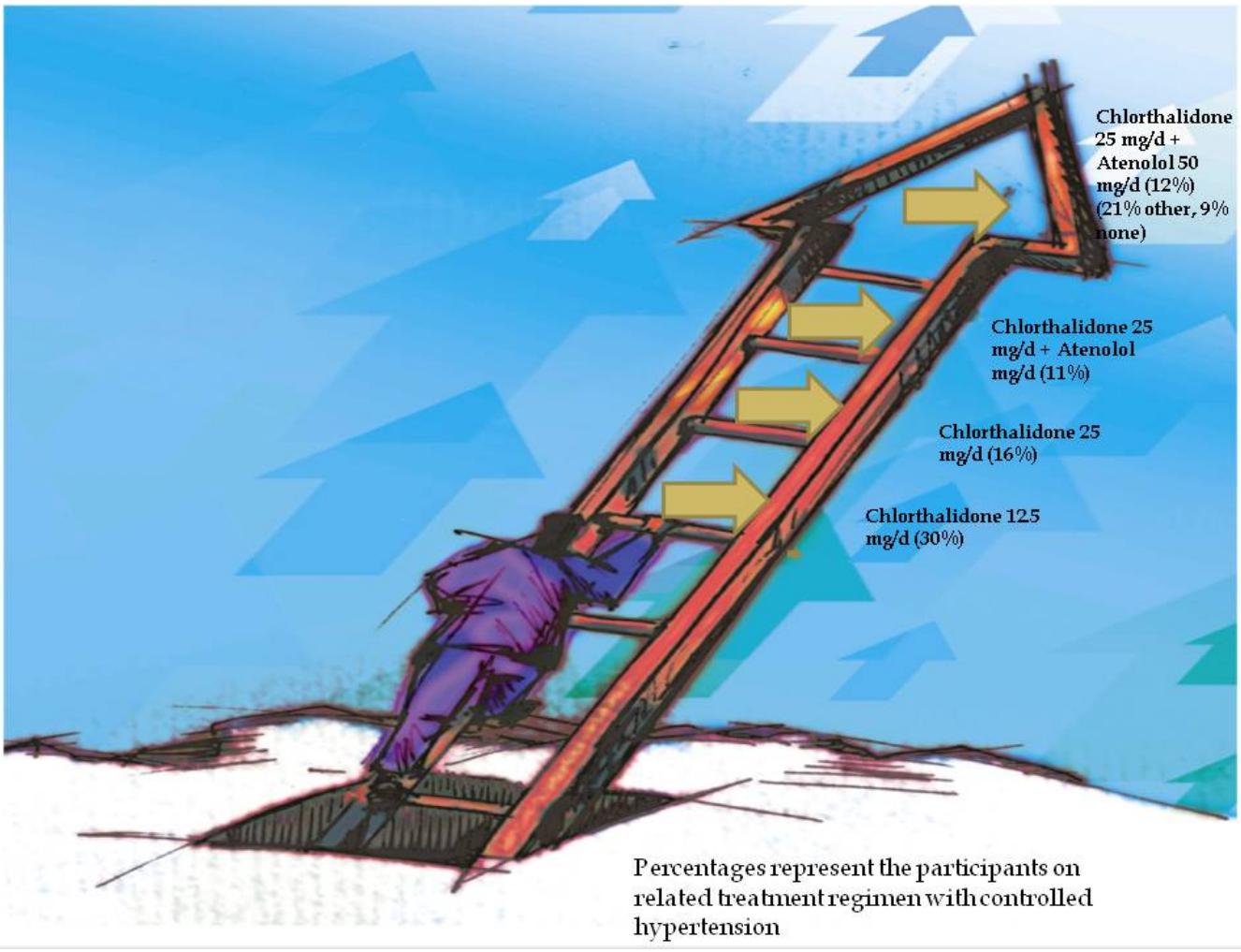
Table 1. *The Search for a Plan: Antihypertensive Therapy in the Very Elderly*

(S. C. R. Group, 1991) (Dahlof et al., 1991) (Beckett et al., 2008)

Study	**Subjects**	**Dosages for Active treatment**	**Focused Outcomes**
Systolic Hypertension in the Elderly Program (SHEP) 1991 Average 4.5 years follow-up	4736 total 2365 active treatment 2731 placebo Average age 72 years systolic blood pressure between 160-219 mmHg and diastolic < 90 mmHg	Step 1: Chlorthalidone 12.5 mg daily Step 2: Chlorthalidone 25 mg daily Step 3: Chlorthalidone 25 mg daily + Atenolol 25 mg daily Step 4: Chlorthalidone 25 mg daily + Atenolol 50 mg daily	36 % stroke reduction total in all age groups Age group: 70-79 with 48 (active treatment) vs. 74 (placebo) stroke events Age group: 80(+) 21 (active treatment) vs. 38 (placebo) stroke events P= 0.0003
Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) 1991 Approximately 5.5 year follow up	1627 total 812 active treatment 815 placebo treatment Systolic 180-230 mm Hg with diastolic 90 mm Hg or a diastolic between 105 and 120 mm Hg.	Atenolol 50 mg Hydrochlorothiazide 25 mg + Amiloride 2.5 mg Metoprolol 100 mg Pindolol 5 mg	Stroke, MI, other cardiovascular death reduction 58 vs. 94 events P= 0.0031 Stroke morbidity/mortality reduction 29 vs. 53 events P = 0.0081 Total Mortality 36 vs. 63 events P = 0.0079
Hypertension in the Very Elderly Trial (HYVET) 2008 Approximately 2 year follow up	3845 total 1933 active treatment 1912 placebo Average age 83.6 years 173.0/90.8 mm Hg average entry blood pressure	Step 1: Indapamide SR 1.5 mg Step 2: Indapamide SR 1.5 mg + Perindopril 2 mg Step 3: Indapamide SR 1.5 mg + Perindopril 4 mg	30% reduction in fatal or nonfatal stroke P = 0.06 39% reduction in death from stroke P= 0.05 21% reduction in all cause mortality P= 0.02 23% reduction in cardiovascular death P= 0.06 64% reduction in death from heart failure P<0.001

Figure 1. *Stepwise approach to treating hypertension in the SHEP Trial* (S.C.R. Group, 1991)



Abstract

Objective: The purpose of this clinical review is to determine any significant benefit to treating hypertension in patients who are nearing 80 years of age and beyond. **Method**: The words used for the search engines were “hypertension”, “hypertension in the elderly”,“treatment of hypertension”, “aged”, “cardiovascular medicine”, “elderly”, “longitudinal study”,”medicine use”, “homebound persons”, “high blood pressure”, “drug utilization”, and “age factors”. The main search engines were MEDLINE, CINAHL, PubMed, and JAAPA. **Results**: Recent research shows that treating patients at least 80 years old, with new onset essential hypertension of at least ≥ 160/90 mm Hg, results in a decrease in stroke events and mortality. First line therapy is a thiazide diuretic with a stepwise approach to increasing dose or adding additional medications if needed. The majority of side effects are mild to moderate electrolyte abnormalities. **Conclusion**: There is a benefit to treating hypertension in the very elderly.