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**ΕΝΗΜΕΡΩΤΙΚΟ ΑΡΘΡΟ**

# Hypertension and Stroke: Evolution and progress in therapies

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## INTRODUCTION

Stroke is the most devastating complication of hypertension, contributing substantially to morbidity and mortality in our population. Many patients, who suffer a stroke, have to spend months and sometimes years in rehabilitation and many others have to live with hemiparesis, hemiplegia, speech abnormalities or other consequences of stroke for the remaining of their life. Furthermore patients who have suffered a stroke are at high risk for recurrence and further deterioration of their quality of life. Strokes can be caused by a number of different mechanisms that include in-situ thrombosis, intracranial/intracerebral hemorrhage or by migration of emboli from the great vessels or the heart. Hypertension is epidemiologically and causally related to all forms of stroke. Longitudinal, epidemiologic studies have shown a linear association of blood pressure with the risk for fatal/non-fatal stroke[1-4]. The association is much stronger with systolic blood pressure, although recent data demonstrate a particularly strong independent association with pulse-pressure. Several mechanisms have been suggested to explain the connection between hypertension and stroke. High blood pressure may accelerate atherosclerosis, which in turn either occludes small blood vessels or becomes the source of emboli which later occlude vessels in the brain. Hypertension may also cause lacunar infarcts, intracerebral hemorrhage, or cerebral white-matter lesions[1]. High blood pressure is a major risk factor for atrial fibrillation, which is a risk factor for stroke, increasing risk 5-fold[2]. Regardless of age or gender, greater incidence of both hemorrhagic and ischemic stroke is associated with higher blood pressure levels[3]. Hypertension contributes to all mechanisms by which stroke occurs – hemorrhagic, thrombotic, or embolic[5-9].

The risk of stroke increases with age and in patients over the age of 65, stroke is the most common vascular complication of hypertension. Recent data indicate that in this age group strokes are more common than myocardial infarctions. Furthermore elderly hypertensive patients often suffer silent lacunar brain infarcts, which eventually lead to brain atrophy and vascular dementia[10].

It is estimated that stroke is the primary cause of death in about 160,000 people every year in the United states alone[6]. Stroke

is four times more likely to produce disability than death, and about one fourth of stroke survivors become permanently disabled. In fact, stroke is the leading cause of serious adult disability, resulting in $30.8 billion in direct health care costs and $18.6 billion in lost productivity in the United States[6]. Hypertension is the strongest modifiable risk factor for stroke, with an estimated attributable risk of more than 49%[8]. A recent meta-analysis of 61 trials that included close to one million people demonstrated positive, consistent, and independent associations between blood pressure and stroke for all age groups[11]. For every 20 mmHg increase in systolic blood pressure or 10 mmHg in diastolic the risk of stroke doubles. About two-thirds of those who have had a first stroke blood pressure is higher than 160/95 mm Hg. For each decade after age 55, stroke risk doubles, and 72% of stroke victims are over the age of 65. With the ever increasing life expectancy in the United States, the incidence of stroke is expected to double in the next three decades.

Besides hypertension, other cardiovascular risk factors contribute to the incidence of stroke. These include smoking (attributable risk 12%), atrial fibrillation (9.4%) and heavy alcohol consumption (4.7%)[4]. There is little epidemiological association between dyslipidemia and stroke, but numerous trials have shown substantial reduction in the risk of stroke with lipid lowering (>25%)[5].

With this background is no surprise that treatment of hypertension was widely anticipated to have a substantial impact on the risk of stroke. Approximately four decades ago, right after effective therapy of hypertension became available, Edward D. Freis from the Veterans Administration Study Group designed and carried out the early studies to assess the effect of hypertension control on cardiovascular complications. Reduction of stroke was among the primary end points. Those early trials[12] demonstrated that treatment of hypertension, compared to placebo prevented 75% of strokes with in a three year period, but it left unclear whether patients with mild elevations of blood pressure be-nefit. Since then, in the 1970s and 80s, numerous other placebo controlled trials, that included over 48,000 patients, further explore the benefits of blood pressure control on health outcomes[13].

Those studies utilized diuretic and beta-blockers based therapies and included younger and older patients. Benefits were noted across all age groups and in aggregate showed a 38% reduction in fatal/nonfatal strokes. High dose diuretics were used in 9 trials and demonstrated a 51% reduction in strokes, low dose diuretics were used in 4 trials and demonstrated 34% reduction, whereas in 4 studies that used beta blocker based treatments, strokes were reduced by 29%[13]. Thus there is today general agreement that treatment of hypertension with diuretics and/or beta-blockers will reduce the risk of stroke by approximately 40%. In absolute numbers the elderly derive greater benefit than younger patients.

In recent years the question has shifted to whether greater benefit can be derived by using newer agents to treat hypertension. Rational for this issue was provided by the many controversies surrounding the potential metabolic effects of diuretics. Thus there was speculation that the benefit from hypertension control might have not been fully realized and newer agents could provide better protection against complications of hypertension, primarily myocardial infarctions. Further more newer therapeutic agents such as Angiotensin Converting Enzyme (ACE) inhibitors and Angiotensin Receptor Blockers (ARB) have been shown to have vascular protective properties in experimental animals that were independent of their blood pressure lowering effect. To explore this possibility several studies were designed to compare the effect of two or more effective therapies of hypertension, on health outcomes, including stroke. Most of those trials compared newer therapies (ACE inhibitors, Calcium Channel Blockers (CCBs) or Angiotensin Receptor Blockers (ARBs) to the old standard therapies with diuretics / beta blockers. Many of these trials have been published but several are still in progress.

In this chapter therefore we'll examine the rational design and results of the most recent and most interesting of those trials with focus the effect on stroke.

**Major Outcomes in High-Risk Hypertensive Patients Randomized to Angiotensin-Converting Enzyme Inhibitor or Calcium Channel Blocker vs Diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial[14].**

## *Background*

It is well established today that long term treatment of hypertension will effectively reduce the

risk of most cardiovascular complication including stroke. Most trials that tested this hypothesis used diuretics and beta blockers compared to placebo. The main objective of the ALLHAT trial was to determine whether treatment with a calcium channel blocker or an angiotensin – converting enzyme inhibitor based regimens lowers the incidence of cardiovascular complications more effectively than a diuretic based regimen.

## *Interpretation*

The ALLHAT study is the largest trial ever done in hypertension and it was conducted between February 1994 and March 2002. Initially more than 42,000 patients were randomized into the trial, but the doxazosin arm was prematurely discontinued due to higher incidence of heart failure and stroke. In the remaining three arms of the study (Chlorothalidone, Lisinopril and amlodipine) 33,357 patients were randomized from 623 centers in North America. Participants were randomly assigned to receive chlorothalidone 12.5 to 25 mg (N=15,255), Amlodipine 2.5 to 10 mg (N=9048) or Lisinopril 10 to 40 mg daily (N=9054). The mean follow up was 4.9 years. The primary outcome (Fatal CHD or non fatal MI) occurred in 2956 patients with no difference between groups. Comparing Amlodipine to chlorothalidone, there was no significant difference in the incidence of stroke although there was a trend in favour of amlodipine. Comparing lisinopril to chlorothalidone however there was a 15% higher incidence of stroke (6.3% vs 5.6%). Heart failure events were lower with chlorothalidone compared to either group.

The authors conclude that thiazide type diuretics are superior in preventing one or more major forms of CVD and are less expensive. Therefore they should be preferred for first step antihy-pertensive therapy.

## *Comment*

This is a landmark study that was set out to answer a very important question: is there benefit in treating patients with hypertension beyond lowering their blood pressure? The study was large enough and powered to adequately address this important question. The results of the study certainly had a great impact not only among practicing physicians, but also in reforming the guidelines. The results are certainly important independent of the interpretation. Although the authors concluded that diuretic therapy is superior compared to therapies with a calcium antagonist or an ACE inhibitor, other interpretations have been proposed and voiced. Results show that patients treated with lisinopril had 15% more strokes than patients receiving a diuretic (Fig. 1, Table 1). However this can be explain in large part by the pressure difference achieved with the use of diuretics. The 5 year blood systolic pressures were 0.8 mmHg higher with amlodipine and 2 mmHg higher with lisinopril (Fig. 2). Although these differences seem

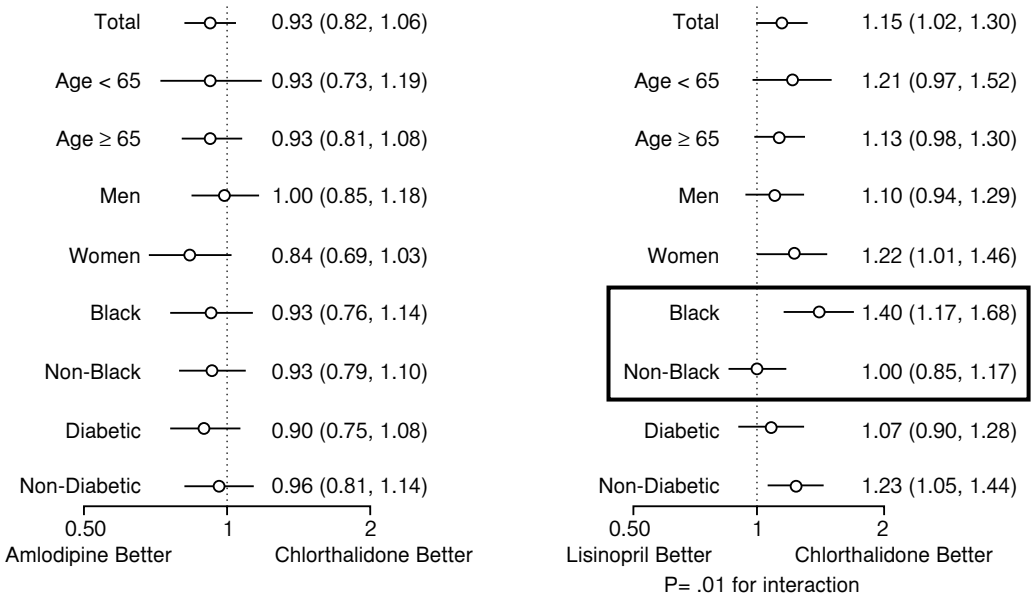



***Fig. 1.*** *Stroke - Subgroups Comparisons - RR (95% Cl).*

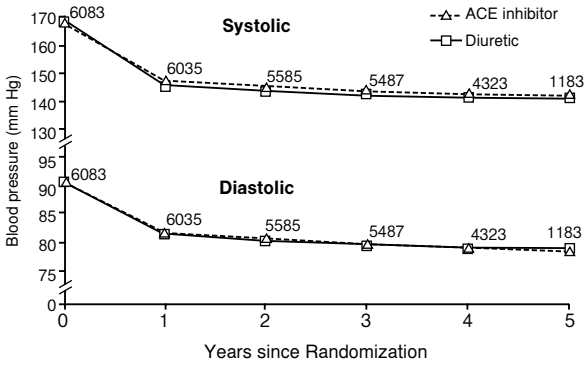



*Fig. 2. Systolic and diastolic blood pressure after randomization. The numbers above the curves indicate numbers of subjects whose blood pressure was measured. ACE denotes angiotensin-converting enzyme.*

small, in large populations such as those included in ALLHAT, can explain the difference in stroke. These results are consistent with prior meta analyses indicating that 2 mmHg difference in blood pressure can explain 15% in the incidence of stroke (Fig. 3,). The ALLHAT results therefore can be viewed slightly different from the conclusion of the authors: diuretics were more effective than the other two therapies in reducing systolic blood pressure and resulted in better prevention of one or more health outcomes. Thus this study proved that diuretics are at least as good as the other antihypertensive agents included in the study, but has not definitely answered the question: is there benefit beyond blood pressure control.

**A Comparison of Outcome with Angiotensin-Converting –Enzyme Inhibitor and Diuretics for Hypertension in Elderly[15].**

## *Background*

This is a second landmark study that addressed the same question: is there benefit in treating patients with hypertension beyond blood pressure control? It has been postulated that blockers of the rennin–angiotensin system may confer benefits beyond blood pressure reduction.

## *Interpretation*

This study was done in Australia in 1594 family practice centers and randomized 6083 patients with hypertension and other risk factors. Patients were randomized to receive an ACE inhibitor or a diuretic and they were followed for an average of 4.1 years. At baseline, the treatment groups were well matched in terms of age, sex, and blood pressure. By the end of the study, blood pressure was reduced by 26/12 mmHg in both groups with no significant difference among treatments (Fig 4). At the end of the follow up period there were 695 cardiovascular events or death in the ACE inhibitor group and 736 in the diuretic group a difference of 11% (p=0.05). The benefit was limited to men. There were 112 strokes in the ACE inhibitor group and 107 in the diuretic group (9% lower incidence with diuretics) (p=NS, Table 1). The authors concluded that initiating treatment with an ACE inhibitor in older subjects with hypertension, parti-

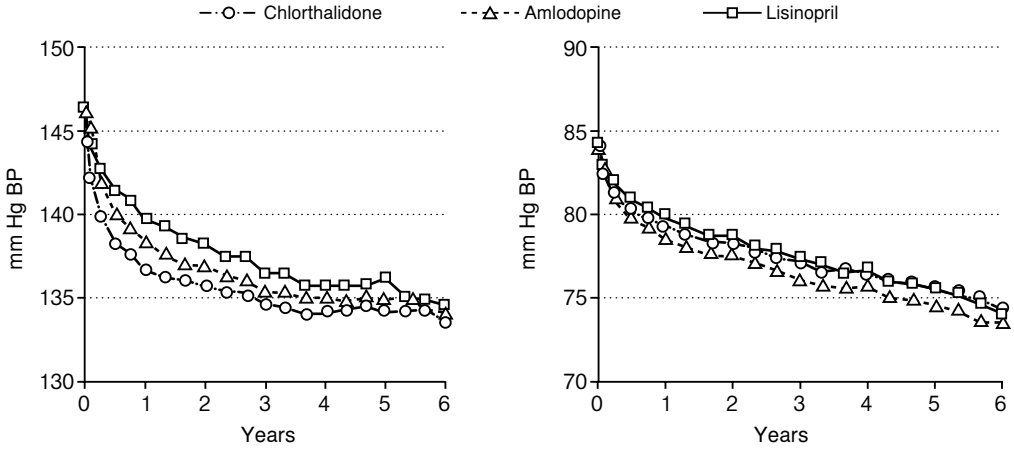


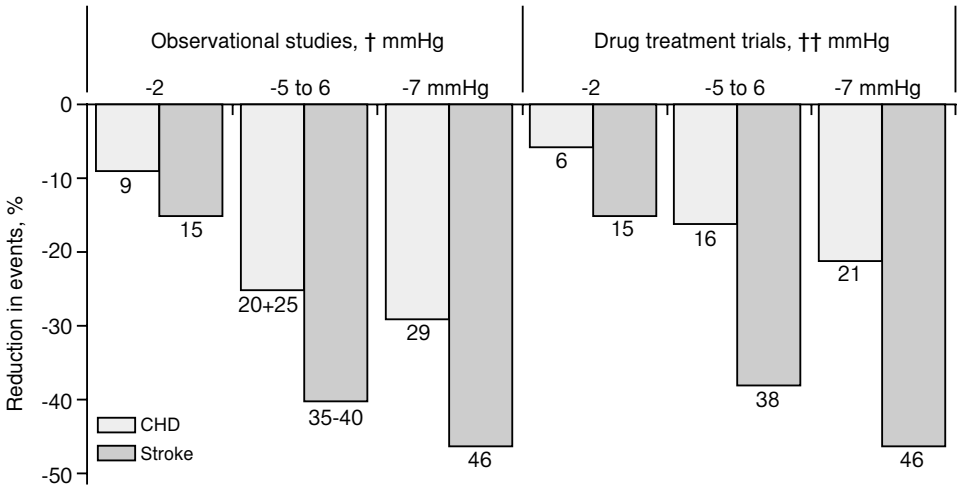

*Fig. 3. BP results by treatment group.*

**Table 1**. Primary end -points and cause-specific first events*

| Event | ACE-Inhibitor Group (n-3044) | | Diuretic Group (n=3039) | | Hazard Ratio (95% Cl) | p Value |
|---|---|---|---|---|---|---|
| | No. of Events | Rate per 1000 Patient-yr | No. of Events | Rate per 1000 Patient-yr | | |
| Primary end -points | | | | | | |
| All cardiovascular evnets or death from arty cause | 695 | 56.1 | 736 | 59.8 | 0.89 (0.79-1.00) | 0.05 |
| First cardiovascular event or death from arty cause | 490 | 41.9 | 529 | 45.7 | 0.89 (0.79-1.01) | 0.06 |
| Death from any cause | 195 | 15.7 | 210 | 17.1 | 0.90 (0.75-1.09) | 0.27 |
| Cause-specific first events | | | | | | |
| First cardiovascular event** | 394 | 33.7 | 429 | 37.1 | 0.88 (0.77-1.01) | 0.07 |
| Coronary event | 173 | 14.3 | 195 | 16.2 | 0.86 (0.70-1.06) | 0.16 |
| Myocardial infarction | 58 | 4.7 | 82 | 6.7 | 0.68 (0.47-0.98) | 0.04 |
| Other cardiovascular event | 134 | 11.0 | 144 | 11.9 | 0.90 (0.71-1.14) | 0.36 |
| Heart failure | 69 | 5,6 | 78 | 6,4 | 0.85 (0.62-1.18) | 0.33 |
| Cerebrovascular event | 152 | 12.5 | 163 | 13.6 | 0.90 (0.73-1.12) | 0.35 |
| Stroke | 112 | 9.2 | 107 | 8.8 | 1.02 (0.78-1.33) | 0.91 |

* Hazard ratios are for the event in the group assigned to angiotensin-converting-enzyme (ACE) inhibitors as compared with the diuretic group are adjusted for age and sex. Cl denotes confidence interval.

** Myocardial infarction is a subcategory of coronary events; heart failure is a subcategory of other cardiovascular events: and stroke is a subcategory of cerebrovascular events. Patients were counted once for each type of first cardiovascular event they had, but patients who had more than one type of event were counted only once for the overall category of first cardiovascular event.




† Data from MacMahonS, et al. *Lancet.* 1990;335:765-774
†† Adapted from Hebert PR, et al. *Arch Intem Med.* 1993;13:578-581
††† Estimated risk reduction

***Fig. 4.*** *Incremental reduction in diastolic blood pressure lowers coronary heart disease and stroke risk.*

cularly men, appears to lead to better outcomes than treatment with diuretic agents.

## *Comment*

This study is important in its own right. It was designed to address the same important questioned asked by ALLHAT: is there benefit beyond blood pressure control? Although the two studies have several similarities they also differ in many different ways that may explain the difference in outcomes: ALLHAT was by far much larger study

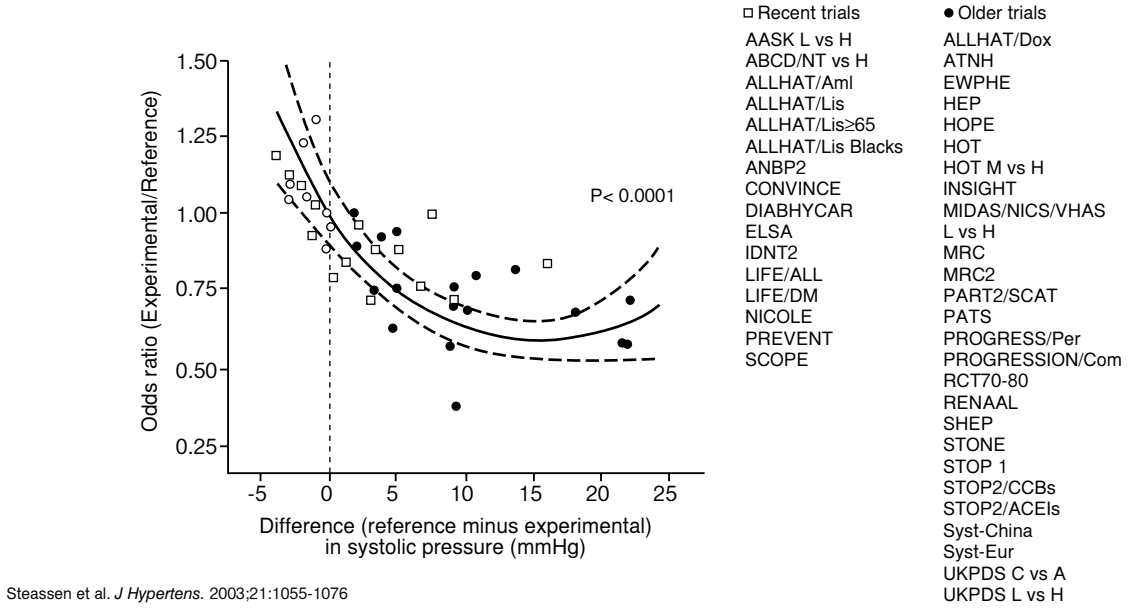



***Fig. 5.*** *Odds ratio for CV events and systolic BP Difference: recent and older trials.*

and included sicker population. The number of events was many times greater in ALLHAT than the Australian study, thus providing much greater power to detect differences.

ALLHAT included a great percentage of African American patients that may respond differently to antihypertensive therapy, such as diuretics and calcium antagonists.

In the ALLHAT study there was a blood presure difference between groups, whereas there was none in the Australian study.

The Australian study was not blinded, thus providing opportunities for bias.

Nevertheless the Australian study was large enough and powered to detect differences between the groups tested. Although the authors conclude that it provides evidence about superior efficacy of ACE inhibitors, this efficacy is by no means conclusive. The difference in the combined endpoint was marginal and limited to men. None of the individual end points was statistically significantly different between groups. The effect on stroke was similar between the two treatment groups, with a trend in favor of diuretic therapy.

**Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomized trial against atenolol[16].**

## *Background*

The question asked by the Losartan Intervention for End Point Reduction in Hypertension Study (LIFE) was similar to ALLHAT and Australian studies. The population included however was different. In LIFE high risk patients with hypertension and left ventricular hypertrophy were included. Left ventricular hypertrophy is a known strong independent indicator of risk of cardiovascular morbidity and death. The aim of the study was to establish whether selective blocking of angiotensin II improves LVH beyond reducing blood pressure and, consequently, reduce cardiovascular morbidity and death.

## *Interpretation*

LIFE was a double-masked, randomized, parallel-group trial of 9193 participants aged 55-80 years with essential hypertension (sitting blood pressure 160-200/ 95-115 mmHg) and LVH ascertained by electrocardiogaphy (ECG). Patients were assigned to once daily losartan-based or atenolol-based antihypertensive treatment for at least 4 years and until 1040 patients had a primary cardiovascular event (death, myocardial infarction, or stroke). Cox regression analysis was used to compare regimens. The study was designed to achieve similar blood pressure reductions in order to better evaluate specific regimen benefits independent of blood pressure. Indeed after a mean follow up of

4.8 years the blood pressure was reduced by 30.2/16.6 and 29.1/16.8 mmHg in the losartan and atenolol treatment groups respectively. The primary composite end point occurred in 508 losartan and 588 atenolol treated patients (p=0.021). Fatal/non-fatal strokes occurred in 232 losartan and 309 atenolol treated patients (p=0.001). Myocardial infarctions and heart failure events were similar among the two arms. The authors concluded that losartan prevents more cardiovascular morbidity and death than atenolol for a similar reduction in blood pressure and that losartan seemed to confer benefits beyond blood pressure reduction.

### *Comment*

The LIFE study is the first large prospective randomized trial to compared two established, effective therapies of hypertension in a high risk population with ECG LVH. Left ventricular hypertrophy has long fascinated clinicians and researchers, because of its strong association with cardiovascular risk and the complex mechanisms of its development and regression. Numerous studies have been designed in the last two decades to assess the degree of mass regression with various therapies assuming that this would confer independent benefit. Indeed a small number of mostly small retrospective trials indicated that regression of LVH is associated with better prognosis. LIFE is the first and only large prospective trial that evaluated the effect of two therapies in this population. Results indicated that treatment with the ARB losartan seemed to confer better vascular protective effect than atenolol, primarily in the prevention of stroke? Like most other large outcome trials LIFE too created a controversy, namely: was the losartan better of atenolol worse in preventing strokes. Many authorities expressed opinions and voiced objections, the fact is however that this large trial demonstrated for the first time than one therapy can be better from another in high risk hypertensives independently of blood pressure. Blockade of AT1 receptors seems to be crucial in the prevention of stroke and this benefit can better be refined certain subgroups as we'll see in later publications.

**The Study on Cognition and Prognosis in the Elderly (SCOPE). Principal results of a randomized double blind intervention trial[17].**

### *Background*

This study was designed to assess the benefit of blood pressure lowering in older patients with mild to moderate hypertension. The primary objective of the study was to assess whether a candesartan based regimen in elderly patients confers better benefit in health outcome reduction than a control regimen.

### *Interpretation*

The study was a prospective, randomized, double blind, parallel group design conducted between 1997 and 2002. A total of 4964 patients age 70 to 89 with systolic pressure of 160 to 179 or diastolic 90 to 99 or both were included in the study from 525 centers in 15 countries. Patients were initially randomized to candesartan or placebo, with other medications added if blood pressure target was not achieved in 3 months. During the study most of the patients in the contro arm received active therapy, mostly diuretics. Blood pressure was reduced by 21.7/10.8 mmHg in the candesartan group and by 18.5/9.2 mmHg in the control group. The primary end point or most individual cardiovascular events were similar between the two treatment groups. However candesartan based treatment reduced non-fatal stroke by 27.8% and all strokes by 23.6% (p=0.056) better than the control group. The authors concluded that a slightly more effective blood pressure reduction with candesartan–based therapy, compared with control reduced resulted in a marked reduction of non-fatal stroke.

### *Comment*

This is an important study primarily because it one of few studies that addressed older patients with mild elevations of blood pressure. It demonstrated that effective therapies that result in only small differences in blood pressure can have a significant impact in the incidence of stroke. That be as it may, the study is not without problems: the initial design was to compare candesartan based therapy to placebo, because at the time it was not clear that older patients with mild hypertension benefit from treatment. Along the way, however and as more data accumulated the study design was shifted and ended up been a comparative study of two treatments. More specifically patients received candesartan alone or in combination with other

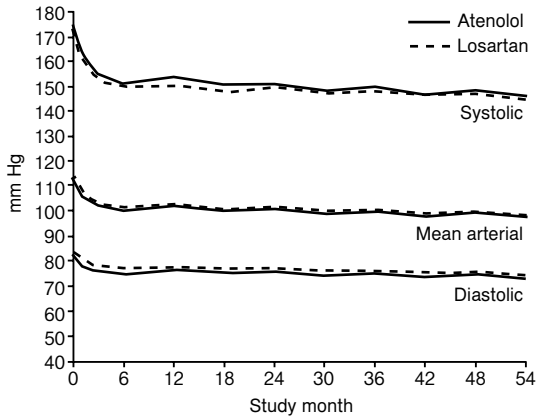



*Fig. 6. ISH-blood pressure development.*

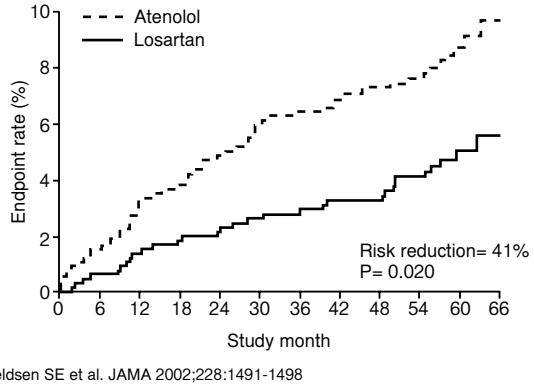



*Fig. 7. ISH-Fatal/Nonfatal stroke.*

drugs, or diuretics alone or in combination with other drugs.

There was a small but significant difference in blood pressure reduction between groups that can explain most of the effect on stroke reduction.

The event rates noted in the study were much less than initially expected, thus underpowering the study.

Nevertheless the conclusion of the study is still important, that treatment of hypertension in this patient population is important and lower blood pressure confers benefits at least in the prevention of stroke.

**Effects of Losartan on Cardiovascular Morbidity and Mortality in Patients with Isolated Systolic Hypertension and Left Ventricular Hypertrophy: A Losartan Intervention for Endpoint reduction (LIFE) substudy[18].**

## *Background*

Isolated Systolic hypertension is a known risk for cardiovascular complications, particularly stroke. This subtype of hypertension is the most common one in elderly populations. Several studies have shown that reduction of systolic blood pressure in these patients is beneficial.

## *Interpretation*

This substudy of LIFE was designed to assess whether an ARB based regimen confers beneficial effects to atenolol in the prevention of cardiovascular complications including stroke. Patients recruited in the study as previously described in the main LIFE trial. Among the 9193 patients included in LIFE, 1326 patients had baseline systolic pressure>160 and diastolic <90 mmHg (Average 174/83 mmHg). Patients also had Electrocardiographic evidence of LVH. Participants were randomized to receive losartan or atenolol monotherapies with HCTZ added as a second medication in both arms for a total of 4.7 years. Blood pressure was reduced by 28/9 mmHg in both groups (Fig. 6). The main outcome (cardiovascular death, non fatal MI or stroke was reduced by 25% more in the losartan group than in the atenolol group. Losartan therapy also resulted in a 41% reduction in fatal and non fatal strokes (p=0.02) (Fig.7), 46% reduction in cardiovascular mortality and 38% reduction in new onset diabetes mellitus. The authors concluded that losartan is superior to atenolol for the treatment of patients with isolated systolic hypertension and left ventricular hypertrophy.

## *Comment*

This is a very important study for many reasons. It is the first comparative study in patients with ISH. It showed a substantial benefit with the use of an ARB as compared to a beta blocker in the prevention of cardiovascular complications primarily stroke, with no difference in blood pressure reduction. The benefit was not limited to stroke, it extended to cardiovascular mortality and new onset diabetes. The benefit was large enough to achieve statistical significance even in a small number of patients.

It has long been speculated that AT1 receptors are instrumental in the development of stroke and that specific blockade of those receptors may provide additional benefit. In fact this effect may be different than ACE inhibitors as it will be com-

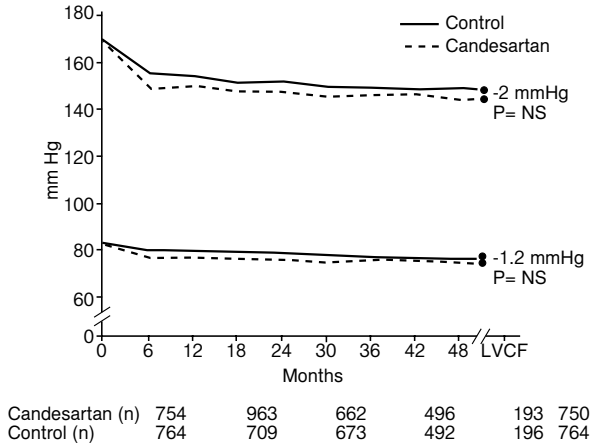



***Fig. 8.*** *Change in blood pressure in SCOPE.*

mented below.

The study also has shortcomings:

It has been speculated that the comparison of losartan to atenolol might have not been the most appropriate one since beta blockers have not been shown to confer benefit from stroke reduction in elderly patients.

This is a retrospective – ad hoc analysis- and patients were not randomized based on the presence of ISH. Thus one cannot exclude the possibility that the baseline risk among the two treatment groups might have been different by chance, although this is rather unlikely.

**Stroke Prevention with the AT1 receptor Blocker Candesartan Cilexitil in Patients with Isolated Systolic Hypertension: The Study on Cognition and Prognosis in the Elderly (SCOPE)[19].**

## *Background*

Isolated systolic hypertension is the predominant form of hypertension in the elderly. In this age group, stroke is the most common cardiovascular complication of hypertension. In experimental animal models, AT1 receptor blockade can prevent stoke independently of blood pressure lowering. This SCOPE substudy tested the hypothesis that candesartan cilexitil can reduce the risk of stroke in elderly patients with ISH.

## *Interpretation*

A total of 4,964 patients aged 70-89 years, with systolic blood pressure 160-179 mmHg, and/or diastolic blood pressure 90-99 mmHg were randomly assigned to the AT1 receptor blocker candesartan or placebo. Open-label active antihypertensive therapy (mostly thiazide diuretics) was added as needed. Active antihypertensive therapy was used in 75% of candesartan and 84% of control patients. Of these patients 1518 had ISH and 3419 combined hypertension (CH). Mean follow-up was 3.7 years.

Of the ISH patients 754 were randomized to candesartan and 764 to placebo. At the end of the study period, systolic (SBP) and diastolic (DBP) blood pressures were reduced by 22.2/5.98 mmHg in the candesartan group and by 20.22/4.82 mmHg in the control group (Diff. 1.98/1.16 mmHg; p=NS for both) (Fig. 8). A total of 20 fatal/non-fatal strokes occurred in the candesartan group and 35 in the control group ($p<0.05$). The stroke rate was 7.2/1000 patient years in the candesartan group and 12.5/1000 patient-years in the control group (Hazard Ratio, HR 0.577, 95% CI 0.333-1.000; p= 0.05) (Fig. 9). Of the 3419 patients with combined hypertension, 1723 were randomized to candesartan and 1696 to placebo. Blood pressure was reduced by 21.37/12.78 mmHg in the candesartan group and by 17.69/11.25 mmHg in the control group (Diff. 3.67/1.53 mmHg, $p<0.001$ for both). Fatal/non-fatal stroke occurred at a rate of 8.0/1000 patient-years in the candesartan group and 10.4/1000 patient-years in the control group (HR 0.844. 95% CI 0.615-1.165; p=NS). Other cardiovascular end points, including fatal/non-fatal MIs, CV death, total mortality or composite end point did not differ

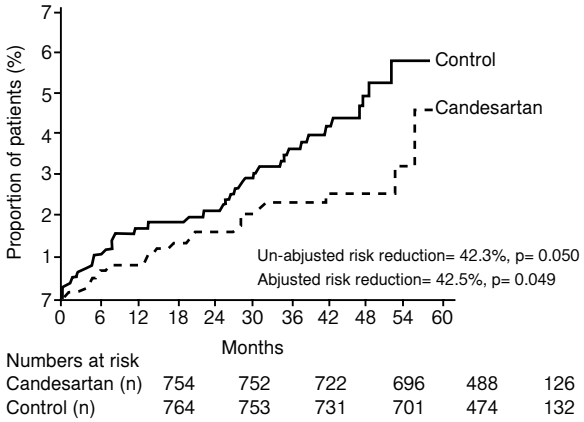



***Fig. 9.*** *Fatal and non-fatal strokes in SCOPE.*

significantly among treatment groups.

**It is concluded that i**n patients with ISH treatment with the AT1 receptor blocker candesartan cilexitil resulted in 42% fewer strokes than the control group despite similar reductions in blood pressure. In contrast no difference was observed in patients with combined systolic diastolic hypertension despite better blood pressure control in patients randomized to the candesartan group

### *Comment*

This is the second study to confer additional benefit from stroke prevention with an ARB as compared to alternative therapy in patients with ISH. Blood pressure was reduced slightly more (p= NS) with candesartan than with medication used in the control group (mostly diuretic), but this difference cannot adequately explain the difference observed in the incidence of stroke. Even if the difference in systolic blood pressure was statistically significant (2 mmHg) would only explain 15% difference in stroke as noted from previous analyses and the ALLHAT study. In this study the overall stroke reduction was 42% lower with candesartan. These results are similar to the ones noted in similar patients with ISH in LIFE. It is interesting that in both studies the ARB reduced stroke substantially more than the comparator. Although there are many similarities among the two studies, there are also several differences: in LIFE patients besides hypertension had also left ventricular hypertrophy. In SCOPE the patient population was older but proved to be much lower risk than the LIFE population. The event rate / 1000 patient years was just about half in SCOPE as compared to LIFE. This may account for the impressive statistics in LIFE and the marginal P values in SCOPE, although percentage wise the difference in event rates was similar between studies.

Experimental data provide support to the hypothesis that blockade of AT1 receptors and overactivity of the AT2 receptors may be instrumental in the prevention and extend of stroke prevention. If both of these events is important, it may explain differences between ACE inhibitors and ARBs in the prevention of stroke.

## CONCLUSIONS

The association of elevated blood pressure with the risk of stroke has been demonstrated beyond any drought. Many observational studies has shown a linear association of both systolic and diastolic blood pressure with the risk of stroke, but more careful analyses have shown that risk to be much higher with systolic blood pressure than diastolic, especially in older patients. A recent meta-regression analysis of 61 trials that included close to one million subjects has shown this association to begin with systolic BP as low as 115 mmHg and diastolic as low as 75 mmHg[11].

Placebo controlled trials done in the 70s and 80s have shown a substantial risk reduction for stroke as well other cardiovascular complications. It has been estimated that even small changes in blood pressure in the population at hand can have substantial impact on the risk for stroke. For instance it has been estimated form observational data that 2 mmHg reduction in diastolic blood pressure or 3-5 mmHg in systolic blood pressure can account for 15-20% reduction in the risk of stroke (Fig. 4). The benefit noted in placebo control interventional

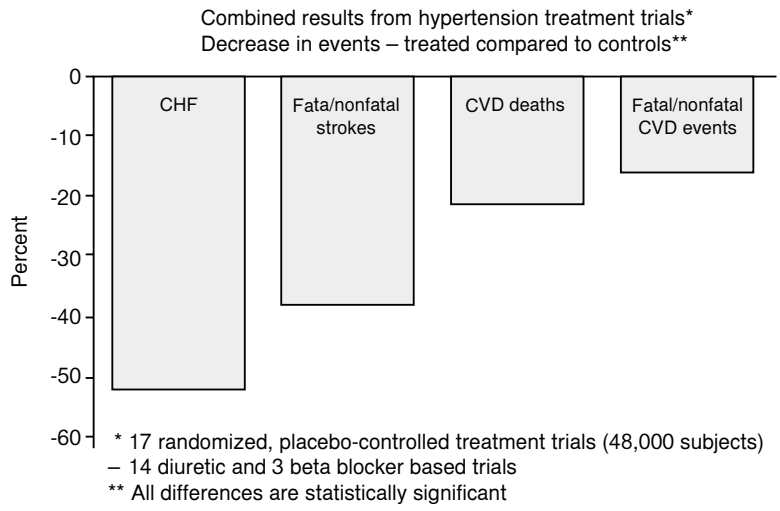



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***Fig. 10.*** *Treatment of hypertension and cardiovascular outcomes: Placebo controlled trials*

trials was indeed 15% for each 2 mmHg reduction is diastolic blood pressure (Fig. 10).

The question asked in recent years is whether reduction of blood pressure with newer untihypertensives such as the blockers of the RAAS or calcium antagonists confer protective effect against stroke beyond blood pressure control. The studies described in this chapter examined primarily these newer agents compared to the older ones, diuretics and beta blockers. The totality of evidence suggests that calcium antagonists and ACE inhibitors, provide for the same blood pressure reduction, similar beneficial effect for stroke prevention, to diuretics.

The introduction in the treatment of hypertension of agents that interrupt the RAAS has opened a new avenue for controlling blood pressure and protecting the heart, the kidney and the brain. Activation of the AT1 receptor by angiotensin II results in vasoconstriction, sodium and fluid retention and eventually blood pressure elevation. AII also has many other effects on the vascular wall the kidney and the heart, the coagulation system and greatly affects lipid metabolism. AT2 receptors provide a counter balance mechanism and regulate the final effect on target organs. Thus it is desirable to block the activation of AT1 receptors and maintain or enhance the activity of the AT2 receptors. This appears to be particularly important in the brain and it may help explain the different effects of ACE inhibitors and ARBs in the prevention of stroke. Several studies that compared the effect of ACE inhibitors to other therapeutic regimens failed to demonstrate benefit beyond the one afforded by blood pressure reduction. These studies include the ALLHAT study, the CAPPP, PROGRESS STOP-2 and others. ARBs on the other hand have been shown in at least two trials to be superior to the comparators ( LIFE, SCOPE) in the prevention of stroke.

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