Randomized Controlled Trials on Hypertension

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Abstract: Numerous randomized controlled trials on hypertension have been conducted since the Veterans Administration (VA) Study on severe hypertension more than 30 years ago. The consensus derived from these trials comprises the following: (1) Lowering of systolic pressure by 10–20 mgHg and of diastolic pressure by 5–10 mgHg reduces cerebrovascular disease by 35–40% and coronary heart disease by 10–15%; (2) A similar degree of beneficial effects is observed in the hypertensive elderly; (3) In primary prevention of cerebrovascular disease, diuretics, β-blockers, Ca-antagonists, and ACE-inhibitors are effective; (4) In secondary prevention of coronary heart disease, β-blockers and ACE-inhibitors are effective; of heart failure, ACE-inhibitors and All-receptor antagonists are effective; and of nephropathy ACE-inhibitors and Ca-antagonists appear to be effective. The results of randomized controlled trials of new drugs such as All-receptor antagonists and conventional drugs are expected to be published soon.

Key words: Hypertension; Randomized controlled trials; Evidence based medicine; Target organ damage

Introduction

Many randomized controlled studies on hypertension have been conducted since the VA Study on severe hypertension was performed more than 30 years ago. The consensus derived from these studies is summarized as follows: (1) Lowering of systolic pressure by 10–20 mgHg and of diastolic pressure by 5–10 mgHg reduces cerebrovascular disease by 35–40% and coronary heart disease by 10–15%; (2) A similar degree of beneficial effects is observed in the hypertensive elderly; (3) The higher the diastolic pressure and the older the patients (but among those younger than 80) are, the higher is the benefits of the blood pressure lowering effect; (4) Diuretics, β-blockers and Ca-antagonists have been demonstrated as effective in pri-
mary prevention of cerebrovascular disease. According to STOP-Hypertension 21 published at the end of 1999, ACE-inhibitors and Ca-antagonists have shown substantially similar effects as conventional diuretics and \( \beta \)-blockers; \( \beta \)-blockers and ACE-inhibitors have been demonstrated as effective in secondary prevention of ischemic heart disease, ACE-inhibitors and \( \beta \)-blockers of heart failure, and ACE-inhibitors and Ca-antagonists of renal dysfunction. A\’s regards heart failure, it is now clear that AII-receptor antagonists show similar benefits as ACE-inhibitors (ELITE II).21

The results of comparative studies on new drugs such as AII-receptor antagonists and conventional drugs are expected to be published successively. The outline of the results of these studies is discussed below.

**Summary of Randomized Controlled Studies on Hypertension**

The result of analysis31 of 17 clinical trials (47,653 patients, mean age, 56; the follow-up period, 4–5 years) in the west such as the study on diuretics and \( \beta \)-blockers by Whelton et al. discussed in the 2000 edition of “Guideline for Treatment of Hypertension” published by the Japanese Society of Hypertension reveals the following.

1. In the group treated with antihypertensives, the risk of developing stroke decreased by 38% and that of ischemic heart disease (IHD) by 16%.

2. The higher the diastolic blood pressure (DBP) was, the higher the benefits of antihypertensive treatments became. In the groups of lower than 110 mmHg, 110–114 mmHg, and above 115 mmHg, the numbers of patients per 1000 in each group for...
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such as diuretics and \( \beta \)-blockers that were used in large scale clinical tests in the past and comparatively new drugs such as ACE-inhibitors, Ca-antagonists, and \( \alpha_1 \)-blockers are now being published. Basically, there are observed no differences in the mortality and morbidity of cardiovascular disease according to the new and the old drugs. Characteristics of these results are discussed below.

(1) In CAPPP,\(^5\) because the blood pressure level at the start was higher in the ACE-inhibitor group than the group of diuretics or \( \beta \)-blocker, the incidence of stroke was higher in the ACE-inhibitor group. However, compared to the groups administered diuretic or \( \beta \)-blocker, ACE-inhibitor restrained development of diabetes mellitus (DM) and decreased the incidences of stroke, myocardial infarct, and cardiovascular death in DM.

(2) In STOP-Hypertension 2,\(^1\) no difference in the morbidity and mortality of cardiovascular disease was observed between the conventional drug group and the new drug group. On the other hand, there were a fewer incidences of myocardial infarction and congestive heart failure in the group dosed ACE-inhibitor than in the Ca-antagonist group.

(3) In INSIGHT 6\) and NORDIL,\(^7\) no difference in the morbidity and mortality of cardiovascular disease was observed between the Ca-antagonist group (sustained release nifedipin and sustained release diltiazem) and the diuretic and \( \beta \)-blocker groups. On the other hand, heart failure increased in the nifedipin group compared to the diuretic group. In the diltiazem group, the incidence of stroke significantly decreased compared to the groups dosed diuretics or \( \beta \)-blockers.

(4) According to the intermediate analysis of ALLHAT study\(^8\) of the United States, \( \alpha_1 \)-blockers and diuretic in the high risk hypertensive group showed similar results regarding the mortality of coronary heart disease.

Comparison of Conventional Anti-hypertensives (diuretics, \( \beta \)-blockers) and New Antihypertensive Drugs (ACE-inhibitors, Ca-antagonists, \( \alpha_1 \)-blockers) (Table 2)

The results of comparative studies on drugs which stroke was prevented were 9, 19, and 35, respectively, and those for whom ischemic heart disease was prevented were 5, 12, and 15, respectively.

(3) The older the patients were, the higher was the efficacy of antihypertensive treatments. The numbers of subjects per 1000 for whom stroke was prevented in the groups of younger than 60 and older than 60 was 9 and 23, respectively, and those for whom IHD was prevented were 5 and 13, respectively.

These results coincide with that of meta-analysis of studies on diuretics and \( \beta \)-blockers published by Collins et al. in 1994 in which stroke decreased by 38% and IHD by 16%, respectively in the treated groups compared to the control groups (Fig. 1).

Historically speaking,

(1) the preventive effect of antihypertensive treatments on mortality and morbidity from cardiovascular risk in the severe and the moderate hypertensions (DBP \( \geq 105 \) mmHg) was demonstrated by the VA study reported in 1970;

(2) the beneficial effect of antihypertensive treatments to reduce cardiovascular risk in mild hypertension (DBP \( \geq 90 \) mmHg) was also demonstrated in many studies such as Australian National Study (1980) and MRC Study (1985);

(3) clinical trials on the hypertensive elderly have advanced in the 1990s and established the efficacy of antihypertensive treatments (Table 1);

(4) in recent years, randomized controlled studies comparing conventional diuretics and \( \beta \)-blockers with new Ca-antagonists, ACE-inhibitors and \( \alpha_1 \)-blockers are being conducted and their results published.
<table>
<thead>
<tr>
<th>Name of trial</th>
<th>EWPHE</th>
<th>HEP</th>
<th>SHEP</th>
<th>STOP</th>
<th>MRC II</th>
<th>STONE</th>
<th>Syst-Eur</th>
<th>Syst-China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of subjects</td>
<td>≥60</td>
<td>60–79</td>
<td>≥60</td>
<td>70–84</td>
<td>65–74</td>
<td>60–79</td>
<td>≥60</td>
<td>≥60</td>
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<tr>
<td>No of subjects</td>
<td>840</td>
<td>884</td>
<td>4,736</td>
<td>1,627</td>
<td>4,396</td>
<td>1,632</td>
<td>4,695</td>
<td>2,394</td>
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<td>Entered BP(mmHg)</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>diastolic</td>
<td>90–119 &amp; 105–120 &amp; &lt;90 &amp; ≥90 or 105–120 &amp; &lt;115 &amp; 296 &amp; &lt;95 &amp; &lt;95</td>
<td></td>
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</tr>
<tr>
<td>Pre-treatment BP</td>
<td>180/101</td>
<td>187/100</td>
<td>177/77</td>
<td>195/102</td>
<td>185/91</td>
<td>168/98</td>
<td>174/86</td>
<td>170/86</td>
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<tr>
<td>Antihypertensive</td>
<td>diuretic</td>
<td>β-blocker</td>
<td>diuretic</td>
<td>1. β-blocker</td>
<td>1. β-blocker</td>
<td>Ca-antagonist</td>
<td>Ca-antagonist</td>
<td>Ca-antagonist</td>
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<tr>
<td>(†:used secondarily)</td>
<td>†methylodopa</td>
<td>†diuretics</td>
<td>†β-blocker</td>
<td>2. diuretics</td>
<td>2. diuretic</td>
<td>†ACE-inhibitor</td>
<td>†ACE-inhibitor</td>
<td>†ACE-inhibitor</td>
</tr>
<tr>
<td>Trial method</td>
<td>dbl. blind</td>
<td>open</td>
<td>dbl. blind</td>
<td>dbl. blind</td>
<td>sgl. blind</td>
<td>sgl. blind</td>
<td>dbl. blind</td>
<td>sgl. blind</td>
</tr>
<tr>
<td>Follow-up (yr)</td>
<td>4.7</td>
<td>4.4</td>
<td>4.5</td>
<td>2.1</td>
<td>5.8</td>
<td>3.0</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Post-treatment BP(mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated group</td>
<td>150/85</td>
<td>162/77</td>
<td>144/68</td>
<td>167/87</td>
<td>152/77</td>
<td>146/85</td>
<td>151/79</td>
<td>150/81</td>
</tr>
<tr>
<td>Control group</td>
<td>171/95</td>
<td>180/88</td>
<td>155/71</td>
<td>186/99</td>
<td>166/83</td>
<td>155/90</td>
<td>161/84</td>
<td>159/84</td>
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<tr>
<td>Effectiveness (relative risk)</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Cerebrovascular</td>
<td>0.64</td>
<td>0.58*</td>
<td>0.67*</td>
<td>0.53*</td>
<td>0.75*</td>
<td>0.43*</td>
<td>0.58*</td>
<td>0.62*</td>
</tr>
<tr>
<td>Coronary heart</td>
<td>0.82</td>
<td>1.03</td>
<td>0.73*</td>
<td>0.87*</td>
<td>0.81</td>
<td>0.43*</td>
<td>0.70*</td>
<td>1.06*</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.78</td>
<td>0.68</td>
<td>0.45*</td>
<td>0.49*</td>
<td>0.32</td>
<td>0.32</td>
<td>0.71</td>
<td>0.42</td>
</tr>
<tr>
<td>All cardiovascular</td>
<td>0.71*</td>
<td>0.76*</td>
<td>0.68*</td>
<td>0.60*</td>
<td>0.83*</td>
<td>0.40*</td>
<td>0.69*</td>
<td>0.63*</td>
</tr>
</tbody>
</table>

*: significantly different.
#: only for myocardial infarction
: BP for HEP and MRC II are estimated values.

(Source: Japanese Society of Hypertension: Guideline for Treatment of Hypertension, 2000 (JSH 2000))
Table 2: Major Randomized Controlled Trials Comparing Conventional Drugs (Diuretics, β-blockers) and New Drugs (ACE-inhibitors, Ca-antagonists, α₁-blockers)

<table>
<thead>
<tr>
<th>Name of trial</th>
<th>Published in</th>
<th>STOP-Hypertension 2 1999, LANCET</th>
<th>INSIGHT 2000, LANCET</th>
<th>NORDIL 2000, LANCET</th>
<th>ALLHAT targeted for 2002</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>Essential hypertension</td>
<td>Elderly hypertension</td>
<td>Hypertension</td>
<td>Hypertension</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Age</td>
<td>25–66</td>
<td>70–84</td>
<td>55–80</td>
<td>50–74</td>
<td>≥55</td>
</tr>
<tr>
<td>No. of subjects</td>
<td>10,985</td>
<td>6,614</td>
<td>6,321</td>
<td>10,881</td>
<td>ca. 40,000 (24,335)</td>
</tr>
<tr>
<td>Drugs</td>
<td>ACE–inhibitor (captopril) vs. diuretics/ β-blockers</td>
<td>β-blockers or diuretics vs. Ca-antagonists (felodipine, isradipine) vs. ACE-inhibitors (enalapril, lisinopril)</td>
<td>Ca-antagonists (sustained release nifedipine) vs. diuretics</td>
<td>Ca-antagonists (sustained release diltiazem) vs. diuretics/ β-blockers</td>
<td>Ca-antagonists (amlodipine) or ACE inhibitors (lisinopril) or α₁-blocker (doxazosin) vs. diuretics (chlofalaide)</td>
</tr>
<tr>
<td>Period of trial</td>
<td>Six years</td>
<td>Four years</td>
<td>Four years</td>
<td>Four &amp; half years</td>
<td>Six (3.3) years</td>
</tr>
<tr>
<td>Method of trial</td>
<td>PROBE*</td>
<td>PROBE*</td>
<td>Double blind</td>
<td>PROBE*</td>
<td>Double blind</td>
</tr>
<tr>
<td>Results</td>
<td>Onset of cardiovascular disease were equal</td>
<td>Results of conventional and new (Ca-antagonist/ACE inhibitor) antihypertensive were equal</td>
<td>Equal to diuretics</td>
<td>Equal to diuretics/ β-blockers</td>
<td>Intermediate analysis (Mar 2000) revealed no difference between the groups in the onset of lethal coronary heart diseases and non-lethal myocardial infarction, but α₁-blocker was found to have elevated the risk of heart failure by two times compared to diuretics, and the test on α₁-blocker was suspended</td>
</tr>
<tr>
<td>Mortality of cardiovascular disease</td>
<td>Onset/ death by cardiovascular disease were equal</td>
<td></td>
<td>Equal to diuretics</td>
<td>Equal to diuretics/ β-blockers</td>
<td></td>
</tr>
<tr>
<td>Other results</td>
<td>Development of stroke ACE inhibitor&gt; conventional drug</td>
<td>Development of DM ACE inhibitor&lt; conventional drug</td>
<td>ACE inhibitors significantly restrained development of myocardial infarction and congestive heart failures compared to Ca antagonists</td>
<td>Heart failure increased in nifedipine group</td>
<td>Stroke decreased in diltiazem group</td>
</tr>
</tbody>
</table>

*Prospective Randomized Open Blinded End-point Study
Results of Studies on Special Populations and Co-existing Diseases

1. Stroke

As mentioned above, antihypertensive treatments are clearly effective in primary prevention, and very recently PROGRESS study showed the secondary prevention by ACE inhibitors. For primary prevention, lowering of blood pressure is basically important and similar results are achieved with any type of antihypertensive drugs (STOP-hypertension 2: diuretics, β-blockers vs. Ca-antagonists • ACE-inhibitors, INSIGHT: nifedipine, GITS vs. diuretic, etc.)

According to the NORDIL study published in 2000, the incidence of stroke decreased significantly in the sustained release diltiazem group compared to the groups of diuretics or β-blockers.

2. Ischemic heart disease (IHD)

Regarding primary prevention, there may be observed a significant decrease in a single study, but meta analysis reveals, as mentioned above, that treatment with antihypertensives such as diuretics and β-blockers can control the onset of IHD by more than 10% and less than 20%.

The effect of β-blocker (without endogenous sympathomimetic stimulating action) has been established for the secondary prevention. There is a report that diltiazem is effective in preventing recurrence in non-Q infarct patients without heart failure.

ACE-inhibitors have been established to inhibit onset of sudden death or heart failure by the remodeling after myocardial infarction.
The J-curve phenomenon (excessive blood pressure lowering may manifest the contrary effect of exacerbating prognosis in IHD) was not observable up to DBP of 80 mmHg according to the result of HOT.9)

3. The hypertensive elderly
(1) As shown in the meta analysis of the hypertensive patients aged 60 and over (Table 1), the antihypertensive treatments basically controls stroke and IHD as in the case of those aged younger than 60. This is similar to the case of systolic blood pressure (SHEP, Syst-Eur, Syst-China).
(2) As for the types of antihypertensives, efficacy of diuretics has been established (EWPHE, STOP-Hypertension, MRC II, SHEP). Efficacy of Ca-antagonists, particularly of long acting dihydropyridine, has been demonstrated (Syst-Eur, Syst-China, STONE, NICS-EH).
(3) In the very elderly subjects (aged 80 and over), benefits of antihypertensive has not yet been established. The result of ongoing HYVET study is awaited.

4. Chronic heart failure
In treating hypertension accompanying chronic heart failure, efficacy of ACE-inhibitors has been established.10) As for β-blockers, beneficial effects of carvedilol (US Carvedilol trial), bisoprolol (CIBIS II), and metoprolol (MERIT-HF) are being established.
Diuretics are also useful, and spironolactone has been demonstrated recently as effective for improving prognosis of severe heart failure.11) AII-receptor antagonists show a similar degree of improvement for prognosis of heart failure as ACE-inhibitors, with their merit of fewer side effects (ELITE II).2)

5. Nephropathy
Hypertension adversely affects prognosis of renal insufficiency, requiring intense blood pressure lowering. If urinary protein is more than 1g/ day, 125/ 75mmHg or lower is the target value (MDRD). WHO/ISH guideline as well as JSH 2000 guideline base its target on this value.
ACE-inhibitors restrain urinary protein in diabetic nephropathy and non-diabetic nephropathy as well as progression of nephropathy.12)

6. Diabetes mellitus
In HOT using Ca-antagonists, there was evidence that lowering blood pressure to the lowest target level (DBP<80mmHg) in diabetic hypertensive patients resulted in lowering risks of cardiovascular events. This is also confirmed in UKPDS using β-blockers and ACE-inhibitors.13)
ACE-inhibitors were confirmed to restrain lowering of renal functions in diabetic nephropathy.
ACE-inhibitors (CA PPP,6 MICRO-HOPE14)), and Ca-antagonists (HOT, Syst-Eur) were effective for the prevention of cardiovascular disease in diabetic patients. Although not randomized controlled studies, there are reports that ACE-inhibitors have more favourable effects on IHD events compared with Ca-antagonists in diabetic patients.

Conclusion
Mega trials on hypertension were discussed. These results or evidences cannot necessarily be applied directly to one’s patients. True evidence-based-medicine (EBM) in daily clinical scene should consider blood pressure levels, severity of disease in individual patients, type and degree of complications and compliances while taking into consideration the result of these randomized controlled studies.

REFERENCES


