Prevention of Stroke and Myocardial Infarction by Amlodipine and Angiotensin Receptor Blockers
A Quantitative Overview

Ji-Guang Wang, Yan Li, Stanley S. Franklin, Michel Safar

Abstract—In the present quantitative overview of outcome trials, we investigated the efficacy of amlodipine or angiotensin receptor blockers in the prevention of stroke and myocardial infarction in patients with hypertension, coronary artery disease, or diabetic nephropathy. The analysis included 12 trials of 94,338 patients. The analysis of trials involving an amlodipine group showed that amlodipine provided more protection against stroke and myocardial infarction than other antihypertensive drugs, including angiotensin receptor blockers (−19%, \( P<0.0001 \) and −7%, \( P=0.03 \)) and placebo (−37%, \( P=0.06 \) and −29%, \( P=0.04 \)). The analysis of trials involving an angiotensin receptor blocker group showed contrasting results between trials versus amlodipine and trials versus other antihypertensive drugs for stroke (+19% versus −25%; \( P<0.0001 \)) and myocardial infarction (+21% versus +1%; \( P=0.03 \)). The results of 3 trials comparing an angiotensin receptor blocker with placebo were neutral (\( P=0.14 \)). The within-trial between-group difference in achieved systolic pressure ranged from −1.1 to +4.7 mm Hg for trials involving an amlodipine group and from −2.8 to +4.0 mm Hg for trials involving an angiotensin receptor blocker group. The metaregression analysis correlating odds ratios with blood pressure differences showed a negative relationship (regression coefficients: −3% to −8%), which reached statistical significance (regression coefficient: −6%; \( P=0.01 \)) for stroke in trials involving an amlodipine group. In conclusion, blood pressure differences largely accounted for cardiovascular outcome. (Hypertension. 2007;50:181-188.)

Key Words: blood pressure ■ clinical trial ■ calcium channel blocker ■ angiotensin receptor blocker ■ stroke ■ myocardial infarction

In a series of previous meta-analyses,1–5 we and others have found that achieved differences in systolic blood pressure may explain most odds ratios in controlled trials of blood pressure-lowering agents in patients with hypertension or other cardiovascular disorders. These analyses included few trials involving angiotensin receptor blockers (ARBs), a relatively new and increasingly used class of antihypertensive agents. In the last few years, several trials investigated ARBs in patients with a broad range of cardiovascular or renal diseases.6–13 A recent meta-analysis challenged the use of ARBs, because these drugs might provide less protection against myocardial infarction than other classes of blood pressure-lowering drugs.14 This finding raised a controversial issue but was not supported by subsequent meta-analyses with similar studies included.15,16 In a recent editorial,17 a combined analysis of 2 trials6–10 comparing ARBs with a calcium channel blocker amlodipine suggested that amlodipine provided more protection against stroke and myocardial infarction than ARBs. In addition, in keeping with previous meta-analyses,1–5 calcium channel blockade by amlodipine also prevented more stroke than angiotensin-converting enzyme (ACE) inhibitors and old drug classes (diuretics and \( \beta \)-blockers).17 However, in these trials, there were significant though small differences in blood pressure between randomized groups.

The CASE-J Trial18 was presented recently at the 21st Scientific Meeting of the International Society of Hypertension (October 2006, Fukuoka, Japan) and did not show any significant difference in stroke or coronary events between amlodipine- and candesartan-based antihypertensive regimens in Japanese patients with hypertension. In the present quantitative overview, we investigated the efficacy of amlodipine or ARBs in the prevention of stroke and myocardial infarction in patients with hypertension, coronary artery disease, or diabetic nephropathy and explored by meta-regression analysis whether there was any benefit or harm beyond blood pressure control for these 2 classes of antihypertensive drugs.
Methods

Acquisition and Selection of Trials
We searched for outcome trials, which involved amlodipine, an ARB, or both in hypertensive patients or in patients with coronary artery disease or diabetic nephropathy. The other criteria for the studies to be included were as follows: a randomized, controlled design; publication in a peer-reviewed journal; assessment of blood pressure and cardiovascular events; follow-up for ≥2 years; and sample size of ≥100. We also accepted large-scale trials, of which the main results had been presented at international meetings with confirmatory information published on the internet.18

We first compared outcomes among patients randomly assigned to initial treatment with amlodipine or ARBs and placebo or other antihypertensive drugs, such as diuretics, β-blockers, ACE inhibitors, or short-acting calcium channel blockers. In analyses for both amlodipine and ARBs, we incorporated trials of head-to-head comparisons between amlodipine and ARBs. For this part of our analysis, we identified 14 trials including 4 (ALLHAT,19,20 ASCOT,21,22 CAMELOT,12 and PREVENT5), 7 (ACCESS,24 DETAIL,11 IRMA2,25 LIFE,25 MOSES,13 RENAA1,7 and SCOPE6), and 3 studies (CASE-J,6 IDNT,6 and VALUE10) involving an amlodipine group, an ARB group, or both groups, respectively. However, we excluded the ACCESS Trial, because the subjects of this study were patients with hypertension within 24 hours of an acute stroke,24 and the IRMA2 Trial, because the number of cardiovascular events was not reported.25 Of the 12 trials in the analysis, the ALLHAT,19 CAMELOT,12 and IDNT6 Trials included 3 randomly assigned groups. Definitions of all trial acronyms are provided in the Appendix.

We then performed meta-regression analyses separately for trials involving amlodipine or ARBs. For trials involving an amlodipine group, we included odds ratios for amlodipine versus a diuretic (ALLHAT/Chlorthalidone),19 a β-blocker (ASCOT/Atenolol),21 ACE inhibitors (ALLHAT/Lisinopril20 and CAMELOT/Enalapril12), ARBs (CASE-J/Candesartan,18 IDNT/IRbesartan5 and VALUE/Val- sartan6), or placebo (IDNT,6 CAMELOT,12 and PREVENT5). For trials involving an ARB group, we included odds ratios for ARBs versus a β-blocker (LIFE/Atenolol),8 an ACE inhibitor (DETAIL/Enalapril),11 a short-acting calcium channel blocker (MOSES/ Nitrendipine13), amlodipine (CASE-J,18 IDNT,6 and VALUE10), or placebo (SCOPE,6 IDNT,6 and RENAA1,7). Outcomes

We based our analysis on the summary statistics reported in the literature1,6–13,19–21,23 or at meetings and available in the internet.19 In all of the trials, outcome results were reported on the basis of an intention-to-treat principle. However, in 7 (ASCOT, CAMELOT, CASE-J, LIFE, MOSES, SCOPE, and VALUE) of the 12 trials, from 6 (0.3%)13 to 85 (0.4%)21 or from 0.3%8,12 to 3.8% (n = 53)13 of patients were excluded from the intention-to-treat analysis because of good clinical practice deficiencies,10,18 blood pressure measurement,21 or other unspecified10 irregularities; withdrawal of consent12,24; or data quality concerns or nondispense of study drugs.9 We extracted from the source documents fatal and nonfatal strokes (excluding transient ischemic attacks) and fatal and nonfatal myocardial infarctions (excluding silent). Starting from published reports, we had no other option than to accept the definitions of events as given by the investigators. For the ALLHAT and ASCOT trials, myocardial infarctions also included coronary deaths.19,21 For the CAMELOT Trial, strokes included transient ischemic attacks, and myocardial infarctions included cardiovascular deaths.12

Statistical Methods

We determined the relative difference from the odds ratios by Zelen’s test and to compute exact 95% CIs.27 In the presence of significant heterogeneity, we applied a random-effects model to compute pooled estimates.28 To permit comparisons with other overviews,11 we also derived the SDs of the pooled odds ratios by analogy with the asymptotic approach by dividing the logarithmically transformed 95% CI by 2×1.96. All reported P values are for 2-sided hypotheses.

We performed separate metaregression analyses for trials involving amlodipine or ARBs and pooled trials with reference treatment of the same class. We used the SAS statistical software (SAS Institute), version 9.1, to correlate odds ratios of amlodipine or an ARB versus reference treatment with the corresponding baseline-adjusted differences in systolic blood pressure between randomized groups. For these calculations, odds ratios were logarithmically transformed. The regression lines were weighted by the inverse of the variance of the individual odds ratios.29 Net treatment effects on blood pressure were determined by subtracting the mean change in the amlodipine or ARB group from the corresponding mean change in the reference group. When a group of trials were pooled, the blood pressure difference was calculated by averaging the between-group blood pressure difference within each trial with the number of randomly assigned patients as a weighting factor. To standardize estimates of relative risk across trials, whenever possible, we computed observed odds ratios with exact 95% CI from 2×2 contingency tables.

Results

Amlodipine Versus Placebo or Other Antihypertensive Drugs
Seven trials with 78 323 randomly assigned patients compared amlodipine with a diuretic (n = 24 303),19 a β-blocker (n = 19 257),21 ACE inhibitors (n = 19 438),12,20 ARBs (n = 21 094),6,10,18 or placebo (n = 3279).6,12,23 Tables 1 and 2 show the characteristics of these trials and randomly assigned patients, respectively. For the pooled analyses, including stroke and myocardial infarction, the P values for heterogeneity did not reach statistical significance (0.12 < P ≤ 0.99; Figure 1).

For actively controlled trials, overall, the pooled analyses showed that amlodipine provided significantly more protection against stroke and myocardial infarction than other classes of antihypertensive drugs. For the 6 trials combined,6,10,12,18–21 the odds ratio was 0.81 (95% CI: 0.75 to 0.87; P < 0.0001) for stroke and 0.93 (95% CI: 0.87 to 0.99; P = 0.03) for myocardial infarction. However, the benefit of amlodipine was more consistent and prominent for stroke than for myocardial infarction. For stroke, the odds ratio was statistically significant regardless of trials versus ARBs (odds ratio: 0.84; 95% CI: 0.73 to 0.97; P = 0.02) or trials versus other antihypertensive drugs (odds ratio: 0.79; 95% CI: 0.72 to 0.87; P < 0.0001). For myocardial infarction, the odds ratio was only significant in trials versus ARBs (odds ratio: 0.83; 95% CI: 0.72 to 0.96; P = 0.01) but not in trials versus other drugs (P = 0.29).

For the placebo-controlled trials, the pooled odds ratios had a size consistent with estimations of previous meta-analyses, but probably because of the relatively small number of events (74 strokes and 159 myocardial infarctions) only reached borderline statistical significance for stroke (odds ratio: 0.63; 95% CI: 0.38 to 1.04; P = 0.06) and myocardial infarction (odds ratio: 0.71; 95% CI: 0.51 to 0.99; P = 0.04).

ARBs Versus Placebo and Other Antihypertensive Drugs
Eight trials with 39 487 randomly assigned patients compared ARBs with a β-blocker (n = 9193),6 an ACE inhibitor (n = 250),11 a short-acting calcium channel blocker (n = 1352),13...
For stroke, because of significant heterogeneity, we contrasted the pooled odds ratios of 3 head-to-head comparison trials of ARBs versus amlodipine and 3 trials versus other antihypertensive drugs (odds ratio: 1.19; 95% CI: 1.03 to 1.38 versus odds ratio: 0.75; 95% CI: 0.64 to 0.89; \( P<0.0001 \)). For myocardial infarction, in spite of insignificant heterogeneity (\( P=0.26 \)), the pooled odds ratios were also significantly different among 3 head-to-head comparison trials of ARBs versus amlodipine and 3 trials versus other antihypertensive

### TABLE 1. Characteristics of Trials

<table>
<thead>
<tr>
<th>Trial Masking</th>
<th>Total No. of Patients</th>
<th>Age, y</th>
<th>SBP/DBP, mm Hg</th>
<th>Disease or Risk Factors</th>
<th>Primary Outcome</th>
<th>Control, mg</th>
<th>Experimental, mg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trials involving amlodipine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALLHAT(^{16,20}) Double</td>
<td>33 357(^*)</td>
<td>( \geq 55 )</td>
<td>140 to 180/90 to 110 or treated ( \geq 160/100 )</td>
<td>1 risk factor</td>
<td>Coronary death + MI</td>
<td>Chlorothalidone (12.5 to 25)</td>
<td>Amlodipine (2.5 to 10) or lisinopril (10 to 40)</td>
</tr>
<tr>
<td>ASCOT(^{21}) Open</td>
<td>19 257</td>
<td>40 to 79</td>
<td>( \geq 160/100 ) or treated ( \geq 140/90 )</td>
<td>3 risk factors</td>
<td>Coronary death + MI</td>
<td>Atenolol (50 to 100)</td>
<td>Placebo</td>
</tr>
<tr>
<td>CAMELOT(^{12}) Double</td>
<td>1991</td>
<td>30 to 70</td>
<td>Untreated or treated ( \leq 100 )</td>
<td>CAD (( \geq 20% ) stenosis)</td>
<td>Coronary death + MI</td>
<td>Atorvastatin (10 to 20)</td>
<td>Amlodipine (5 to 10)</td>
</tr>
<tr>
<td>PREVENT(^{23}) Double</td>
<td>825</td>
<td>30 to 80</td>
<td>Untreated or treated ( \leq 95 )</td>
<td>CAD (( \geq 30% ) stenosis)</td>
<td>Rate of coronary atherosclerosis</td>
<td>Placebo</td>
<td></td>
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<tr>
<td><strong>Trials involving an ARB</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>LIFE(^{8}) Double</td>
<td>9193</td>
<td>55 to 80</td>
<td>160 to 200/95 to 115</td>
<td>ECG LVH</td>
<td>CV death + MI + stroke</td>
<td>Atenolol (50 to 100)</td>
<td>Losartan (50 to 100)</td>
</tr>
<tr>
<td>DETAIL(^{11}) Double</td>
<td>250</td>
<td>35 to 80</td>
<td>Treated &lt;180/95 on ACEI</td>
<td>2DM + nephropathy(</td>
<td>) Change in GFR</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>MOSES(^{13}) Open</td>
<td>1352</td>
<td>Any(</td>
<td>)</td>
<td>( \geq 140/90 ) or treated</td>
<td>CBV</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>SCOPE(^{9}) Double</td>
<td>4937</td>
<td>70 to 89</td>
<td>Untreated or treated</td>
<td>No</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RENAAL(^{7}) Double</td>
<td>1513</td>
<td>31 to 70</td>
<td>160 to 179/90 to 99</td>
<td>2DM + nephropathy(</td>
<td>) All-cause death + ESRD + DBSC</td>
<td>Placebo</td>
<td></td>
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<tr>
<td><strong>Trials involving amlodipine and an ARB</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>IDNT(^{6}) Double</td>
<td>1715</td>
<td>30 to 70</td>
<td>( \geq 135/85 ) or treated</td>
<td>2DM + nephropathy(</td>
<td>) All-cause death + ESRD + DBSC</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>VALUE(^{10}) Double</td>
<td>15 245</td>
<td>( \geq 50 )</td>
<td>160 to 210/( \geq 115 ) or treated</td>
<td>CV diseases or risk factors(</td>
<td>) MI + HF</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>CASE-J(^{18}) Open</td>
<td>4703</td>
<td>20 to 85</td>
<td>( \leq 140/90 ) or ( \geq 70 ) y ( \geq 160/90 )</td>
<td>1 disease or risk factor</td>
<td>CV death + MI + AP + CR + HF + stroke + PAD</td>
<td>Amlodipine (2.5 to 10)</td>
<td>Candesartan (4 to 12)</td>
</tr>
</tbody>
</table>

ACEI indicates ACE inhibitor; AP, angina pectoris; CAD, coronary artery disease; CBV, cerebrovascular events including stroke and transient ischemic attack; CR, coronary revascularization; CV, cardiovascular; DBSC, doubling of baseline serum creatinine; ESRD, end-stage renal disease; GFR, glomerular filtration rate; HCTZ, hydrochlorothiazide; HF, heart failure; MI, myocardial infarction; PAD, peripheral arterial disease; RCA, resuscitated cardiac arrest; SBP/DBP, systolic/diastolic blood pressure; VE, vascular events. Acronyms of trials are explained in Appendix section.

\(*\)Total number of patients in the chlorthalidone, amlodipine, and lisinopril groups.

\(|\)A urinary albumin excretion rate (mean of 3 consecutive overnight values) between 11 and 999 \( \mu \)g/min, with 2 values >10 \( \mu \)g/min.

\(|\)A total of 84% of the SCOPE patients allocated placebo were on open-label antihypertensive treatment, mainly diuretics (66%) or \( \beta \)-blockers (26%).

\(|\)Age at onset of cerebrovascular events <80 years.

\(|\)The presence on 2 occasions of a ratio of urinary albumin in milligrams per liter to urinary creatinine in grams per liter from a first morning specimen of \( \geq 300 \) (or a rate of urinary protein excretion of at least 0.5 g per day).

\(|\)Urinary albumin excretion \( \geq 900 \) mg/24 hours.

\(|\)The presence of cardiovascular risk factors or disease according to an algorithm based on age and sex.

For stroke, because of significant heterogeneity, we contrasted the pooled odds ratios of 3 head-to-head comparison trials of ARBs versus amlodipine and 3 trials versus other antihypertensive drugs (odds ratio: 1.19; 95% CI: 1.03 to 1.38 versus odds ratio: 0.75; 95% CI: 0.64 to 0.89; \( P<0.0001 \)). For myocardial infarction, in spite of insignificant heterogeneity (\( P=0.26 \)), the pooled odds ratios were also significantly different among 3 head-to-head comparison trials of ARBs versus amlodipine and 3 trials versus other antihypertensive drugs (odds ratio: 1.19; 95% CI: 1.03 to 1.38 versus odds ratio: 0.75; 95% CI: 0.64 to 0.89; \( P<0.0001 \)).
drugs (odds ratio: 1.21; 95% CI: 1.04 to 1.40 versus odds ratio: 1.01; 95% CI: 0.84 to 1.22; \( P=0.03 \)). The combined result of the 3 placebo-controlled trials was neutral for stroke (\( P=0.14 \)) and for myocardial infarction (\( P=0.46 \)).

**Metaregression Analysis**

We plotted odds ratios for both amlodipine and ARB trials in the same figure but performed metaregression analyses separately for trials involving an amlodipine group and those involving an ARB group (Figure 3). The within-trial, between-group difference in systolic blood pressure ranged from \(-1.1 \text{ mm Hg}^{19} \) to \(+4.0 \text{ mm Hg} \) for trials involving an amlodipine group and from \(-2.8 \text{ mm Hg}^{19} \) to \(+3.2 \text{ mm Hg}^{15} \) for trials involving ARBs. For the trials involving ARBs, the metaregression line was not significant for either stroke or myocardial infarction (\( P>0.22 \) for the 2 intercepts and \( P>0.20 \) for the 2 regression coefficients).

**Discussion**

The main finding of our overview was that calcium channel blockade by the use of amlodipine substantially reduced the risk of stroke and myocardial infarction. The benefit of initial treatment with this drug versus other antihypertensive drugs could be largely, though not entirely, explained by blood pressure differences between randomized groups of trials. The performance of ARBs seemed to some extent dependent on the comparator drug. When compared with an ACE inhibitor or particularly with a \( \beta \)-blocker or a short-acting calcium channel blocker, ARBs showed superiority for stroke prevention and similarly for coronary prevention. When contrasted with a long-acting calcium channel blocker, amlodipine, ARBs were less effective in lowering blood pressure and also demonstrated inferiority for the prevention of stroke and myocardial infarction.

Our overview has to be interpreted within the context of its limitations. As in all meta-analyses that start from published summary statistics, we achieved less standardization than is attainable in quantitative overviews based on individual patient data. Thus, the participants’ characteristics may have influenced our estimates of benefits or risks, as well as the definition and validation of end points in individual trials.

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**TABLE 2. Characteristics of Patients**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients*</th>
<th>Mean Age, y</th>
<th>Mean At entry</th>
<th>Difference During Follow-Up†</th>
<th>Percentage of Patients</th>
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<td>Control</td>
<td>Experimental*</td>
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<tr>
<td>ALLHAT chlorthalidone(^{19} )</td>
<td>15255</td>
<td>9048</td>
<td>67</td>
<td>146/84</td>
<td>47</td>
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<tr>
<td>ASCOT atenolol(^{22} )</td>
<td>9618</td>
<td>9639</td>
<td>63</td>
<td>164/95</td>
<td>23</td>
</tr>
<tr>
<td>ALLHAT lisinopril(^{19,20} )</td>
<td>9054</td>
<td>9048</td>
<td>67</td>
<td>146/84</td>
<td>47</td>
</tr>
<tr>
<td>CAMELOT enalapril(^{11} )</td>
<td>673</td>
<td>663</td>
<td>58</td>
<td>129/77</td>
<td>25</td>
</tr>
<tr>
<td>CAMELOT placebo(^{12} )</td>
<td>655</td>
<td>663</td>
<td>57</td>
<td>129/78</td>
<td>25</td>
</tr>
<tr>
<td>PREVENT placebo(^{23} )</td>
<td>408</td>
<td>417</td>
<td>57</td>
<td>129/79</td>
<td>25</td>
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<tr>
<td>IDNT placebo(^{6} )</td>
<td>569</td>
<td>567</td>
<td>59</td>
<td>159/87</td>
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**Table Continued**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients*</th>
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<th>Percentage of Patients</th>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>LIFE atenolol(^{6} )</td>
<td>4588</td>
<td>4605</td>
<td>67</td>
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<tr>
<td>DETAIL enalapril(^{11} )</td>
<td>130</td>
<td>120</td>
<td>61</td>
</tr>
<tr>
<td>MOSES nitrendipine(^{13} )</td>
<td>671</td>
<td>681</td>
<td>68</td>
</tr>
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<td>SCOPE placebo(^{6} )</td>
<td>2460</td>
<td>2477</td>
<td>76</td>
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<tr>
<td>IDNT placebo(^{6} )</td>
<td>569</td>
<td>679</td>
<td>59</td>
</tr>
<tr>
<td>RENAAL placebo(^{7} )</td>
<td>762</td>
<td>751</td>
<td>60</td>
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<table>
<thead>
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<tr>
<td>IDNT(^{6} )</td>
<td>567</td>
<td>579</td>
<td>59</td>
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<tr>
<td>VALUE(^{10} )</td>
<td>7649</td>
<td>7596</td>
<td>67</td>
</tr>
<tr>
<td>CASE-(^{18} )</td>
<td>2349</td>
<td>2354</td>
<td>64</td>
</tr>
</tbody>
</table>

CAD indicates coronary artery disease; HCTZ, hydrochlorothiazide; MI, myocardial infarction; SBP/DBP, systolic/diastolic blood pressure. Acronyms of trials are explained in the Appendix section.

*The experimental group was arbitrarily defined as the ARB group for the comparisons between amlodipine and ARBs.
†Positive values indicate tighter blood pressure control in the experimental group.
‡Median or mean.
§Significant difference in achieved blood pressure between randomized groups.
¶Stroke includes transient ischemic attack.
#Fasting blood glucose concentration = 200 mg/dL.

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Indeed, the trial with an open design tended to produce results in favor of the tested drug. Blinded end point evaluation cannot avoid overreporting or underreporting of events by investigators. Second, there is limited trial evidence for ARBs in hypertension, especially for the comparison with ACE inhibitors, which might decrease the validity of the meta-analysis in general and metaregression analysis in particular. The ongoing ONTARGET Trial might provide some additional evidence. More studies are definitely required, considering the huge number of patients with hypertension who are currently exposed to various ARBs. Third, this analysis was restricted to trials in patients with hypertension or in patients with coronary artery disease or diabetic nephropathy, of whom the majority also had high blood pressure. Thus, the findings of this analysis cannot be directly extrapolated to other patient populations, such as those with acute myocardial infarction or congestive heart failure. Fourth, a few trials, such as ALLHAT, ASCOT, and VALUE, are much larger than the other studies included in our analysis and, hence, in pooled analyses may overwhelm the small trials. However, the results of the small
trials appear qualitatively similar to those of the large trials so that the inequality of sample size probably does not greatly affect the overall results. In addition, we did not include in our analysis heart failure as an outcome, mainly because the diagnostic procedure for heart failure is inconsistent across trials, and because heart failure is not always precisely reported.

Our findings on amlodipine versus diuretics, β-blockers, or ACE inhibitors are in keeping with the results of previous meta-analyses, which showed that calcium channel blockade in general provides more protection against stroke and that amlodipine in particular provides similar protection against myocardial infarction. For the comparison between amlodipine and ARBs, the pooled results remained virtually unaltered from the combined results of 2 trials after adding on data of the CASE-J Trial. Amlodipine provided 16% and 17% more protection against stroke and myocardial infarction than ARBs, in the presence of 1.5 mm Hg of systolic pressure difference favoring amlodipine. The 1.5 mm Hg of difference in systolic blood pressure may account for most if not all of the difference in stroke and probably also in myocardial infarction.

Calcium channel blockade prevents intima-media thickening. This might contribute to the observed 11% of blood pressure–independent benefit of amlodipine on stroke. However, it is also possible that the benefit is only independent of blood pressure measured in the clinic, in the daytime, or at the brachial artery, but not necessarily independent of blood pressure obtained at home, for 24 hours, especially at night or at the aorta. There is some evidence that the latter pressures might be more predictive of cardiovascular outcome than the former pressure parameters. The ASCOT Conduit Artery Function Evaluation substudy showed that amlodipine-based regimen, compared with atenolol-based treatment, reduced central systolic pressure by 4.3 mm Hg, despite similar influence on brachial pressure. The ambulatory blood pressure–monitoring substudy of the ASCOT Trial reported recently in meetings that amlodipine-based regimen, compared with atenolol-based treatment, significantly reduced nighttime pressure. However, whether the difference in nighttime pressure or in central pressure estimated by a transfer function could account for outcome remains to be elucidated.

Our analysis on ARBs focused on trials in hypertension in the presence or absence of cardiovascular disease or diabetic nephropathy, and, hence, differed slightly from previous analyses on this issue. In general, ARBs provided average protection against stroke but inferior protection against myocardial infarction. The contrasting results between trials

Figure 3. Odds ratios for fatal and nonfatal stroke (left) and fatal and nonfatal myocardial infarction (right) in relation to corresponding differences in systolic blood pressure. Odds ratios were calculated for the amlodipine group vs placebo or other classes of antihypertensive drugs including ARBs (dots) or for the angiotensin receptor group vs placebo or other classes of antihypertensive drugs including amlodipine (squares). Blood pressure differences were obtained by subtracting the mean change in the amlodipine or ARB group from the corresponding mean change in the reference group. When a group of trials was pooled, the blood pressure difference was calculated by averaging the between-group blood pressure difference within each trial with the number of randomly assigned patients as weighting factor. Positive values indicate tighter blood pressure control in the experimental group. The regression line was drawn for trials involving an amlodipine group and weighted by the inverse of the variance of the individual odds ratios. For further explanation, see the Statistical Methods section.
versus amlodipine and trials versus other drugs suggest that
the outcome effect of ARBs depended on the comparator
drug. This dependency, however, can still be attributable
to blood pressure differences (~1.1 versus +0.7 mm Hg;
Δ=1.8 mm Hg), despite insignificant results in the meta-
regression analysis. Ancillary pharmacological properties of
certain drugs might also play a part. For instance, amlodipine
prevents intima–media thickening.32

According to Fournier’s hypothesis, angiotensin type 1
receptor blockade is neuroprotective by the upregulation of
the angiotensin type 2 receptor in the brain.36 However, there
is insufficient evidence of randomized trials, in spite of
significant findings in the MOSES13 and LIFE trials.3 The
MOSES Trial had an open design, small sample size
(n=1352), and high exclusion rate after randomization
(6.8%). The LIFE Study compared losartan with atenolol,
which had been repeatedly shown inferior to other classes of
antihypertensive drugs, especially in stroke prevention,36,37
needless to say the significant, though small, blood pressure
difference in favor of losartan.2 In addition, the estimation of
the inferiority of ARBs in coronary prevention was relatively
small (+13%), with a wide CI (+1 to +30%). This new class
of drugs requires more randomized trials, especially in
patients with hypertension.

Conclusions

The conclusions of our previous meta-analyses1–3 that blood
pressure differences largely account for cardiovascular out-
come remain valid, consistently and strongly emphasizing the
desirability of tight blood pressure control. There is some
evidence that certain drugs or classes of drugs might confer
small blood pressure–independent superior or inferior influ-
ence on certain outcome measures or in certain populations.
However, before we incorporate the tiny evidence into
clinical guidelines, more studies are required.

Perspectives

As evidenced by ALLHAT19,20 and ASCOT,21 the 2 largest-
ever trials in hypertension, amlodipine-based antihyperten-
svive regimen, compared with other drug regimens, might
confer more outcome benefit, possibly by lowering central
systolic pressure14 or ambulatory pressure over 24 hours. The
latter hypothesis should be tested against antihypertensive
drugs, preferably long acting and other than β-blockers,
especially atenolol. Because ARBs are gaining market in
most countries, there is urgent need for well-designed and
well-conducted randomized, controlled trials. For instance,
ARBs should be compared with ACE inhibitors to test
whether the former are neuroprotective in acute stroke pa-
tients and to test whether the latter are more protective against
myocardial infarction in patients with hypertension at high
cardiac risk.

Appendix

Acronyms of Trials

ACCESS (Acute Candesartan CilExetil therapy in Stroke Survi-
vors39); ALLHAT (Antihypertensive and Lipid-Lowering treatment
to prevent Heart Attack Trial31,32); ALLHAT/Diu (Antihypertensive
and Lipid-Lowering treatment to prevent Heart Attack Trial–Amlo-
dipine Versus Chlorthalidone33); ASCOT (Anglo-Scandinavian Car-
diovascular Outcomes Trial34,35); CAMELOT (Comparison of AMloidipine
versus Enalapril to Limit Occurrences of Thrombosis36); CASE-J
(Candesartan Antihypertensive Survival Evaluation in Japan37);
DETAIL (Diabetes Exposed to Telmisartan And enalapril Study13);
IDNT (Irbesartan Diabetic Nephropathy Trial in patients with type-2
diabetes mellitus40); IRMA2 (Irbesartan in patients with type-2
diabetes and Microalbuminuria Study38); LIFE (Losartan Inter-
vention For Endpoint reduction in hypertension13); MOSES (MOrbidity
and mortality after Stroke, Eprosartan compared with nitrendipine
for Secondary prevention13); PREVENT (Prospective Randomized
Evaluation of the Vascular Effects Norvasc Trial39); RENAAAL
(Reduction of Endpoints in Noninsulin-dependent diabetes mellitus
with the Angiotensin II Antagonist Losartan37); SCOPE (Study on
COgnition and Prognosis in the Elderly40); and VALUE (Valsartan
Antihypertensive Long-term Use Evaluation Trial41).

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Meta-Analysis of Amlodipine and ARB Trials 187

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