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

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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 β-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 metaregression analysis whether there was any benefit or harm beyond blood pressure control for these 2 classes of antihypertensive drugs.

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Methods

Acquisition and Selection of Trials

We searched for outcome trials, which involved amlopidine, 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 amlopidine 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 amlopidine and ARBs, we incorporated trials of head-to-head comparisons among amlopidine and ARBs. For this part of our analysis, we identified 14 trials involving 4 (ALLHAT,19,20 ASCOT,21,22 CAMELOT,12 and PREVENT23), 7 (ACCESS,24 DETAIL,11 IRMA2,25 LIFE,2 MOSES,13 RENAA1,7 and SCOPE9), and 3 studies (CASE-J,18 IDNT,6 and VALUE10) involving an amlopidine 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 amlopidine or ARBs. For trials involving an amlopidine group, we included odds ratios for amlopidine versus a diuretic (ALLHAT/Chlorthalidone),19 a β-blocker (ASCOT/Atenolol),21 ACE inhibitors (ALLHAT/Lisinopril19 and CAMELOT/Enalapril12), ARBs (CASE-J/Candesartan,18 IDNT/Irbesartan5 and VALUE/Val- sartan10), or placebo.6,12,23 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), amlopidine (CASE-J,18 IDNT,6 and VALUE10), or placebo (SCOPE,10 IDNT,6 and RENAA1,7).

Outcomes

We based our analysis on the summary statistics reported in the literature6–13,19–21,23 or at meetings and available on the internet.18 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%)12 to 85 (0.4%)21 or from 0.3%8,12 to 3.8% (n=250),11 a short-acting calcium channel blocker (n=1352),13 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 amlopidine or ARBs and placebo trials with reference treatment of the same class. We used the SAS statistical software (SAS Institute), version 9.1, to correlate odds ratios of amlopidine 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 amlopidine 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

Amlopidine Versus Placebo or Other Antihypertensive Drugs

Seven trials with 78 323 randomly assigned patients compared amlopidine 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 amlopidine 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 amlopidine 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),5 an ACE inhibitor (n=250),11 a short-acting calcium channel blocker (n=1352),13

Statistical Methods

We determined the relative difference from the odds ratios in published literature.26 We used StatXact for Windows (CYTEL Software Corporation), version 4.0, to check the homogeneity of 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,1,1 we also derived the SDs of the
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.
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 mm Hg to 4.7 mm Hg for trials involving an amlodipine group and from −2.8 mm Hg to 1.6 mm Hg for trials involving an ARB group (Table 2 and Figure 3).

The metaregression analysis correling the odds ratios with the corresponding within-trial differences in systolic blood pressure showed negative relationship (regression coefficients: −3% to −8%). For the trials involving an amlodipine group, the metaregression line was significant and linear for stroke (regression coefficient±SE: −6±2%; P=0.01) but not statistically significant for myocardial infarction (regression coefficient±SE: −3±2%, P=0.18). For stroke, blood pressure differences accounted for 90% of the variance of individual odds ratios, and the intercept of the metaregression line also reached statistical significance (intercept±SE: 89±33%; P=0.007), indicating an 11% benefit in outcome beyond systolic pressure differences between randomized groups. 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 findings 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 β-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.
Indeed, the trial with an open design tended to produce results in favor of the tested drug.\textsuperscript{13} 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.\textsuperscript{31} 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,\textsuperscript{19,20} ASCOT,\textsuperscript{21} and VALUE,\textsuperscript{10} 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

Figure 1. Effects of antihypertensive treatment on stroke (left) and myocardial infarction (right) in trials comparing amlodipine with placebo or other classes of antihypertensive drugs, including ARBs. \textsuperscript{[a]} Odds ratios in trials, with a size proportional to the number of events. 95% CIs for individual trials are denoted by lines and those for the pooled odds ratios by diamonds. Where appropriate, the comparator drug is given after the acronym of each trial. Acronyms of trials are explained in a separate section of this article.

Figure 2. Effects of antihypertensive treatment on stroke (left) and myocardial infarction (right) in trials comparing ARBs with placebo or other classes of antihypertensive drugs, including amlodipine. \textsuperscript{*} A random-effects model was used. For further explanation, see Figure 1.
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,1–5 which showed that calcium channel blockade in general provides more protection against stroke2–5 and that amlodipine in particular provides similar protection against myocardial infarction.1 For the comparison between amlodipine and ARBs, the pooled results remained virtually unaltered from the combined results of 2 trials17 after adding on data of the CASE-J Trial.18 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.32 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.33 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.34 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.15,16 In general, ARBs provided average protection against stroke but inferior protection against myocardial infarction. The contrasting results between trials
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 inima–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.33 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 (3.8%).13 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 that the significant, though small, blood pressure difference in favor of losartan.8 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 outcome 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 influence 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 antihypertensive regimen, compared with other drug regimens, might confer more outcome benefit, possibly by lowering central systolic pressure54 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 patients 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 Survivors); ALLHAT (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial); ALLHAT/Diu (Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial–Amlodipine Versus Chlorthalidone); ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial); CAMELOT (Comparison of Amlodipine versus Enalapril to Limit Occurrences of Thrombosis); CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan); DETAIL (Diabetes Exposed to Telmisartan And enalapril Study); IDNT (Irbesartan Diabetic Nephropathy Trial in patients with type-2 diabetes mellitus); IRMA2 (Irbesartan in patients with type-2 diabetes and Microalbuminuria Study); LIFE (Losartan Intervention For Endpoint reduction in hypertension); MOSES (MOrbidity and mortality after Stroke, Eprosartan compared with nitrendipine for Secondary prevention); PREVENT (Prospective Randomized Evaluation of the Vascular Effects Norvasc Trial); RENAAL (Reduction of Endpoint in Noninsulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan); SCOPE (Study on Cognition and Prognosis in the Elderly); and VALUE (Valsartan Antihypertensive Long-term Use Evaluation Trial).


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