Review Article

Should Atenolol Still Be Recommended as First-Line Therapy for Primary Hypertension?

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In addition to blood pressure control, antihypertensive treatment should reduce the incidence of cardiovascular morbidity and mortality as well as total mortality. For four decades, beta-blockers have been widely used for the treatment of hypertension and are still proposed as first-line drugs in national and international guidelines.[1,2] Numerous prospective, randomised studies have established beyond any doubt the efficacy of beta-blockers in patients with coronary artery disease (angina or history of myocardial infarction),[3-5] congestive heart failure[6-8] or hypertrophic cardiomyopathy.[9] Newer vasodilating drugs, such as carvedilol, bisoprolol and nebivolol, which have a more favorable haemodynamic profile, may be more beneficial.[10-12] This view is supported by the Carvedilol or Metoprolol European Trial (COMET) study in patients with congestive heart failure, in which carvedilol was superior to metoprolol in reducing morbidity and mortality.[10]

However, the efficacy of beta-blockers in the treatment of primary hypertension has been challenged.[13-16] Studies with beta-blockers apart from atenolol are surprisingly few, with few clinical events, so the results are inconclusive.[17-19] Moreover, atenolol is one of the most popular beta-blockers and has often been used as a reference drug in randomised controlled trials in arterial hypertension. During the last four years, three mega-trials have been published comparing atenolol to active antihypertensive treatment.[20-22] Hence, the aim of this study was to systematically review and analyse the effect of atenolol on cardiovascular and all-cause mortality, stroke and myocardial infarction in hypertensive patients.

Methods

The eligibility criteria for inclusion in this meta-analysis were: a) treatment of primary hypertension, b) randomised controlled trial, c) atenolol as first line antihypertensive drug in at least 50% of all patients in one treatment group, and d) outcome data for stroke, myocardial infarction, as well as cardiovascular and all-cause mortality. Studies were identified through a search of the Cochrane Library and PubMed. Data from the studies that fulfilled the criteria were entered into the Cochrane Collaboration review manager package (RevMan 4.2). Homogeneity between the studies was assessed using the χ^2 test and the chosen summary statistical variable was the reduction in relative risk (RR).

Results

We identified 19 randomised controlled trials in which atenolol was used in one of the

treatment groups in hypertensive patients. Five studies were excluded because atenolol was one of many first-line drugs in the same treatment arm.[23-27] Two studies were excluded because atenolol was a second-line drug.[28,29] The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT)[30] was also excluded, since atenolol was one of the three second-line drugs. Furthermore, the Heart Attack Primary Prevention in Hypertension Trial (HAPPHY),[31] in which hypertensive patients were randomised to treatment with a beta-blocker (atenolol or metoprolol) or a diuretic, was excluded because the results were published together, with the exception of all-cause mortality, for which data have been published for atenolol versus diuretic.

The remaining ten studies were divided into two main groups. The first group included studies comparing atenolol with placebo and the second group studies comparing atenolol with other antihypertensive drugs. The Medical Research Council trial of treatment of hypertension in older adults (MRC old)[32] had three treatment groups comparing atenolol with a thiazide diuretic and with placebo and was therefore included in both main groups.

The first group included four studies:

1. Treatment of Hypertension in Elderly Patients in primary care (HEP).[33] Hypertensive patients, aged 60-79 years, were randomised to treatment with atenolol (n=419) or placebo (n=465). Bendroflumethiazide was added in 60% of the patients in the atenolol group. There was a 30% reduction in the rate of fatal stroke in the treatment group compared with the control group ($p<0.025$). All strokes (fatal and non-fatal) in the treatment group were lower in comparison to the control group (RR 0.57, 95% confidence interval [CI] 0.34-0.96, $p<0.03$). The blood pressure difference between the two groups was also considerable in this study (18/11 mmHg) and was higher than in other studies. The incidence of myocardial infarction (RR 1.02, 95% CI 0.66-1.59), cardiovascular mortality (RR 0.78, 95% CI 0.51-1.17) and all-cause mortality (RR 0.97, 95% CI 0.70-1.33) were unaffected by treatment. Since patients were not randomised to different treatment groups, it was not possible to compare the response to the beta-blocker and the diuretic.
2. Medical Research Council trial of treatment of hypertension in older adults (MRC old).[32] Hypertensive patients, aged 65-74 years, were randomised to treatment with atenolol (n=1102) or amiloride plus hydrochlorothiazide (n=1081) or placebo (n=2213). The blood pressure difference between atenolol and placebo was 13.5/7.0 mmHg. There was no significant difference between atenolol and placebo in the incidence of stroke (RR 0.84, 95% CI 0.62-1.14), myocardial infarction (RR 1.01, 95% CI 0.78-1.31), cardiovascular mortality (RR 1.06, 95% CI 0.84-1.34) or all-cause mortality (RR 1.06, 95% CI 0.90-1.27). The blood pressure difference between atenolol and diuretic was +1.0/-0.5 mmHg. In comparison to the diuretic group the atenolol group had more strokes (RR 1.22, 95% CI 0.83-1.79), more myocardial infarctions (RR 1.63, 95% CI 1.15-2.32), higher cardiovascular mortality (RR 1.41, 95% CI 1.04-1.91) and higher all-cause mortality (RR 1.22, 95% CI 0.99-1.51). The diuretic group had significantly reduced risks of stroke, coronary events and all cardiovascular events compared to the placebo group. The beta-blocker group failed to show a significant reduction in these endpoints.
3. Trial of secondary prevention with atenolol after transient ischaemic attack or non-disabling ischaemic stroke (Dutch TIA Trial).[34] Aspirin-treated patients with transient ischaemic attack (TIA) or non-disabling ischaemic stroke were randomised to 50 mg atenolol daily (n=732) or placebo (n=741). Not all patients were hypertensive, but baseline mean blood pressure was 157/91 mmHg. The blood pressure difference between the two groups was modest (5.8/2.9 mmHg). Fewer patients in the atenolol group had a stroke (RR 0.85, 95% CI 0.60-1.21), but more patients had a myocardial infarction (RR 1.14, 95% CI 0.75-1.72). Cardiovascular mortality was higher in the atenolol group (RR 1.26, 95% CI 0.80-1.97) and so was all-cause mortality (RR 1.12, 95% CI 0.79-1.57). This study neither confirms nor rules out that atenolol prevents important vascular events in patients after transient ischaemic attack or non-disabling ischaemic stroke.
4. Tenormin after Stroke and TIA (TEST).[35] Patients with previous TIA or minor stroke and blood pressure >140/85 mmHg were randomised to treatment with atenolol (n=372) or placebo (n=348). In the atenolol group 81 patients had a stroke, in comparison to 75 patients in the placebo group (RR 1.01, 95% CI 0.77-1.33), while 29 and 36 patients, respectively, had a myocardial infarction (RR 0.75, 95% CI 0.47-1.20). Cardiovascular mortality was lower in the atenolol group (RR 0.82, 95% CI 0.53-1.26) and so was all-cause mortality (RR 0.80, 95% CI 0.56-1.12).

The blood pressure difference between the two groups was modest (4/3 mmHg).

The second group included six studies:

1. Medical Research Council trial of treatment of hypertension in older adults (MRC old).[32] The data comparing atenolol and diuretic have been analysed above.
2. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes (UK Prospective Diabetes Study Group).[36] Hypertensive patients with type 2 diabetes were randomised to treatment with atenolol or captopril, aiming at a blood pressure of <150/<85 mmHg (n=1148). Of the 758 patients allocated to tight control of blood pressure, 400 were allocated to captopril and 358 to atenolol, while 390 patients were allocated to less tight control of blood pressure. Captopril and atenolol were equally effective in reducing blood pressure and the incidence of diabetic complications. In the two groups with tight control of blood pressure (atenolol vs. captopril), there was no significant difference in the incidence of stroke (RR 0.90, 95% CI 0.48-1.69), myocardial infarction (RR 0.84, 95% CI 0.59-1.20), cardiovascular mortality (RR 0.74, 95% CI 0.49-1.14) and all-cause mortality (RR 0.88, 95% CI 0.64-1.20). This study provided no evidence that either drug has any specific beneficial or deleterious effect, suggesting that in patients with type 2 diabetes the main goal must be the tight control of blood pressure.
3. The European Lacidipine Study on Atherosclerosis (ELSA).[37] The primary aim of this study was to compare, in hypertensive patients, the effects of a 4-year treatment based on either lacidipine (n=1177) or atenolol (n=1157) on an index of carotid atherosclerosis: the mean of the maximum intima-media thicknesses (IMT) in far walls of common carotids and bifurcations. The yearly IMT progression rate was 0.0145 mm/y in atenolol-treated and 0.0087 mm/y in lacidipine-treated patients (40% reduction; p=0.0073). Although 24-hour ambulatory blood pressure changes were greater with atenolol (10/9 mmHg) than with lacidipine (7/5 mmHg), no significant difference between treatments was found in the incidence of stroke (RR 1.58, 95% CI 0.69-3.64), myocardial infarction (RR 0.96, 95% CI 0.50-1.85), cardiovascular mortality (RR 2.03, 95% CI 0.61-6.74) or all-cause mortality (RR 1.33, 95% CI 0.65-2.73).
4. The Losartan Intervention For Endpoint reduction in hypertension study (LIFE).[20] Hypertensive patients, aged 55-80 years, with left ventricular hypertrophy were randomised to treatment with losartan (n=4605) or atenolol (n=4588). Blood pressure fell by 30.2/16.6 mmHg (SD 18.5/10.1) and 29.1/16.8 mmHg (SD 19.2/10.1) in the losartan and atenolol groups, respectively. Left ventricular hypertrophy was significantly reduced in the losartan group (p<0.0001). Losartan was better than atenolol in reducing the frequency of the primary composite endpoint (RR 0.87, 95% CI 0.77-0.96, p=0.021). This difference was due mainly to the lower incidence of fatal or non-fatal stroke in the losartan group (RR 0.75, 95% CI 0.63-0.89, p=0.001). There was no significant difference in the incidence of myocardial infarction, although more patients in the losartan group suffered a myocardial infarction (RR 1.07, 95% CI 0.88-1.31, p=0.491). Cardiovascular mortality was lower in the losartan group (RR 0.89, 95% CI 0.73-1.07, p=0.206) and so was all-cause mortality (RR 0.90, 95% CI 0.78-1.03, p=0.128). Furthermore, losartan, in comparison with atenolol, reduced the incidence of stroke by 21% in the subgroup of patients with type 2 diabetes and by 41% in the subgroup with isolated systolic hypertension. Losartan seems to confer benefits beyond reduction in blood pressure.
5. The International Verapamil-Trandolapril Study (INVEST).[21] Hypertensive patients, aged 50 years or older, with coronary artery disease were randomised to treatment with verapamil sustained release (n=11,267) or atenolol (n=11,309). Trandolapril and/or hydrochlorothiazide were administered to achieve blood pressure control. Trandolapril was also recommended for all patients with heart failure, diabetes, or renal impairment. After a follow-up of two years, there was no statistically significant difference between the two groups in the incidence of stroke (RR 0.88, 95% CI 0.72-1.07), myocardial infarction (RR 1.03, 95% CI 0.90-1.17), cardiovascular mortality (RR 1.00, 95% CI 0.88-1.14) or all-cause mortality (RR 0.98, 95% CI 0.90-1.07). Two year blood pressure control was similar between groups.
6. The Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA).[22] Hypertensive patients, aged 40-79 years, with at least three other cardiovascular risk factors but no previous history of coronary heart disease, were randomised to either treatment with amlodipine adding perindopril as required (amlodipine-based regimen, n=9639) or atenolol adding bendroflumethiazide and potassium as required (atenolol-based regi-

men, n=9618). The study was stopped prematurely after 5.5 years' median follow-up. Blood pressure was reduced more effectively on the amlodipine-based regimen, with an accumulated mean in-trial systolic difference of 2.7 mmHg. The amlodipine-based regimen reduced the primary combined endpoint by 10% (p=0.1052). Fewer individuals on the amlodipine-regimen had fatal and nonfatal stroke (RR 0.77, 95% CI 0.66-0.89, p=0.0003) and myocardial infarction (RR 0.87, 95% CI 0.76-1.00, p=0.0458). Cardiovascular mortality was lower on the amlodipine-based regimen (RR 0.76, 95% CI 0.65-0.90, p=0.001) and so was the all-cause mortality (RR 0.89, 95% CI 0.81-0.99, p=0.0247). The amlodipine-based regimen prevented more major cardiovascular events than the atenolol-based regimen.

Discussion

The present meta-analysis shows that, despite the fact that the blood pressure lowering effect of atenolol is not less than that of other antihypertensive drugs, there were significant outcome differences between atenolol and other drugs in the six studies comprising 56,301 patients followed-up for a mean of 5.14 years (Table 1). The comparison of atenolol with other antihypertensive drugs has shown a significantly higher risk of stroke with atenolol (RR 1.27, 95% CI 1.16-1.38, p=0.0004). Moreover, cardiovascular mortality was significantly higher with atenolol treatment (RR 1.13, 95% CI 1.03-1.23, p=0.008) and so was all-cause mortality (RR 1.07, 95% CI 1.01-1.14, p=0.02). The risk of myocardial infarction tended to be higher with atenolol treatment than with other active treatment (RR 1.02, 95% CI 0.95-1.11, p=0.55) (Figure 1).

The results of this meta-analysis have been greatly enhanced after the publication of the ASCOT-BPLA study.[22] This was a large study involving 19,257 hypertensive patients with at least three additional risk factors but no previous history of coronary heart disease. ASCOT-BPLA was stopped prematurely because it was no longer ethically justifiable to continue the patients on the less efficacious comparator treatment. The amlodipine-based regimen was more effective in reducing cardiovascular events than the atenolol-based regimen. The favourable result with the amlodipine-based regimen could not be explained only by the 2.7 mmHg difference achieved in systolic blood pressure in comparison to the atenolol-based regimen.[38] Based on long-term observational data,[39] this difference in systolic blood pressure should translate into a difference in rates of stroke of about 11% and in rates of coronary events of about 8%. These

Table 1. Studies included in the meta-analysis.

Study acronym (year)	Follow up	Number of patients	Mean age (years)	Atenolol dose (mg)	Comparison drug	Atenolol SBP/DBP (mmHg)
Atenolol vs. placebo						
HEP (1986)[33]	4.4	884	68.8	100	Placebo	-18.0/-11.0
MRC old (1992)[32]	5.8	3,315	70.3	50-100	Placebo	-13.5/-7.0
DUTCH TIA (1993)[34]	2.6	1,473	52%>65	50	Placebo	-5.8/-2.9
TEST (1995)[35]	2.6	720	70.4	50	Placebo	-4.0/-3.0
Total	3.85	6,392	69.8*			
Atenolol vs. other antihypertensive drugs						
MRC old (1992)[32]	5.8	2,183	70.3	50-100	HCTZ 25 mg	-1.0/0.5
UKPDS (1998)[36]	9.0	758	56.2	50-100	Captopril 50-100 mg	-1.0/-1.0
ELSA (2002)[37]	3.75	2,334	56.0	50-100	Lacidipine 4-6 mg	-0.2/0.1
LIFE (2002)[20]	4.8	9,193	66.9	50-100	Losartan 50-100 mg	1.1/0.2
INVEST (2003)[21]	2.0	22,576	66.0	25-200	Verapamil SR 120-480 mg	-0.3/-0.2
ASCOT-BPLA (2005)[22]	5.5	19,257	63.0	50-100	Amlodipine 5-10 mg	2.7/1.9
Total	5.14	56,301	63.0			

DBP – diastolic blood pressure; HCTZ – hydrochlorothiazide; SBP – systolic blood pressure; Verapamil SR – Verpamil sustained release.
*Excluding the DUTCH TIA trial.

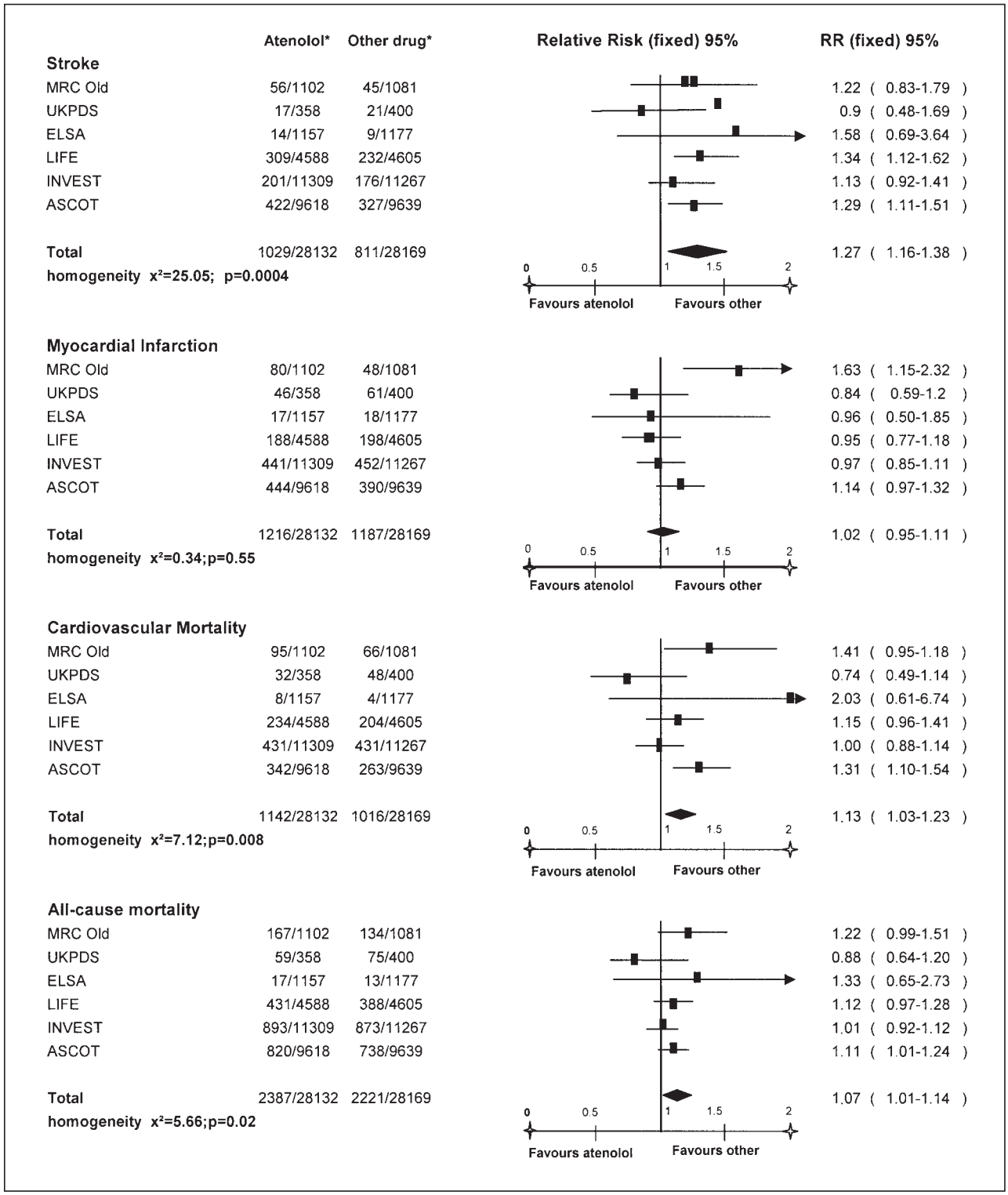

Figure 1. Outcome data for atenolol versus other antihypertensive drugs.
*number of patients with events / total number of patients.

proportions contrast with the actual differences of 23% and 14%, respectively, reported in ASCOT-BPLA.

Another important finding of LIFE and ASCOT-BPLA was the reduction of new-onset diabetes with losartan and amlodipine in comparison with atenolol.

In LIFE, losartan reduced the incidence of new-onset diabetes by 25% in comparison with atenolol (RR 0.75, 95% CI 0.63-0.88). In ASCOT-BPLA, the amlodipine-based regimen reduced the incidence of new-onset diabetes by 30% in comparison with the atenolol-based regimen (RR 0.70, 95% CI 0.63-0.78). However, this difference could be partially attributed to the addition of perindopril to the amlodipine-based regimen, since it has been shown that angiotensin-converting enzyme inhibitors reduce the incidence of new-onset diabetes in comparison with placebo or other antihypertensive drugs.[30,40-42] The occurrence of new diabetes has been reported to portend a risk for subsequent cardiovascular disease that is not dissimilar to that of previously known diabetes.[43,44]

It is noteworthy that the data from four studies comparing atenolol with placebo have not shown superiority of atenolol, despite major differences in blood pressure lowering. In these studies comprising 6392 patients, who were followed-up for a mean of 3.85 years (Table 1), there were no significant differences between atenolol and placebo in the risk of myocardial infarction (RR 0.99, 95% CI 0.83-1.19, p=0.95), cardiovascular mortality (RR 0.99, 95% CI 0.83-1.18, p=0.81), and all-cause mortality (RR 1.01, 95% CI 0.84-1.15, p=0.79). The risk of stroke tended to be lower in the atenolol group than in controls (RR 0.96, 95% CI 0.80-1.16, p=0.744) (Figure 2). This result is mainly due to the HEP study,[30] in which atenolol reduced the risk of stroke by 43% in comparison with controls. However, in this study, a diuretic was added in 60% of the patients in the atenolol group. The blood pressure difference between the two groups was also considerable in the HEP study (18/11 mmHg), and was greater than in other studies. In another classic study, the Dutch TIA trial,[34] 1473 patients who had had either a stroke or a transient ischaemic attack and were already on aspirin were randomised to atenolol or placebo. Although blood pressure was lowered effectively with atenolol when compared with placebo, there was absolutely no effect in terms of outcome (e.g. death or fatal and nonfatal stroke). In addition, side effects such as impotence, hypotension, bradycardia, dizziness, and cold extremities were almost twice as common with atenolol.

Because atenolol reduces blood pressure to the same extent as other antihypertensive drugs, the question arises about possible mechanisms to explain the findings of the present meta-analysis. Several studies have shown differences in the haemodynamic effects of atenolol in comparison with other antihypertensive drugs. In an acute study, both ramipril and atenolol reduced blood pressure, and the diastolic pressure fall was similar in the brachial artery and aorta, but the systolic pressure fall for ramipril was significantly greater than for atenolol (by 5.2 mmHg, $p<0.0001$) in the aorta compared with the brachial artery.[45]

Systolic blood pressure is not accurately recorded by measurement of arterial pressure at the brachial artery.[46] The peak systolic blood pressure represents only one point on the systolic pulse wave and takes little notice of the duration of the systolic period or the shape of the systolic wave. In addition, the significant pressure related to cardiac function and work is the pressure at the origin of the aorta. The heart expels blood against this pressure. The diastolic pressure in the brachial artery is a close approximation to the central aortic diastolic pressure, which is 1 to 2 mmHg higher. However, brachial artery systolic pressure is not a good estimate of the central aortic systolic pressure.

In young healthy individuals, the central aortic systolic pressure is much lower than the brachial artery systolic pressure.[47] This is the result of the reflected wave, which returns to the central aorta late in systole with little amplification of the aortic pressure. However, it has returned to the brachial artery during contraction, leading to amplification of the brachial artery systolic pressure, which is higher than the central aortic systolic pressure.[48,49] As blood vessels become stiff, the pulse wave is transmitted more rapidly and returns to the heart during contraction, resulting in a greater augmentation of the central aortic systolic pressure.[50,51] Other factors, such as slow heart rate, can also affect pulse wave velocity and augmentation of central aortic systolic pressure.[52] Treatment with atenolol reduces brachial blood pressure, but does not lower central aortic systolic pressure as much as treatment with angiotensin-converting enzyme inhibitors (perindopril, enalapril), calcium channel blockers (felodipine, amlodipine) and hydrochlorothiazide.[53] Therapy based on typical blood pressure measurements may overestimate the effect of atenolol on central aortic systolic pressure and underestimate the effectiveness of other antihypertensive drugs. The Conduit Artery Function Evaluation (CAFE) study, a sub-study of ASCOT, has shown that despite similar brachial systolic blood pressures between the amlodipine-based regimen and the atenolol-based regimen, there were statistically significant reductions in central aortic pressures with the amlodipine-based regimen.[54] In addition, while metoprolol blunted the rapid

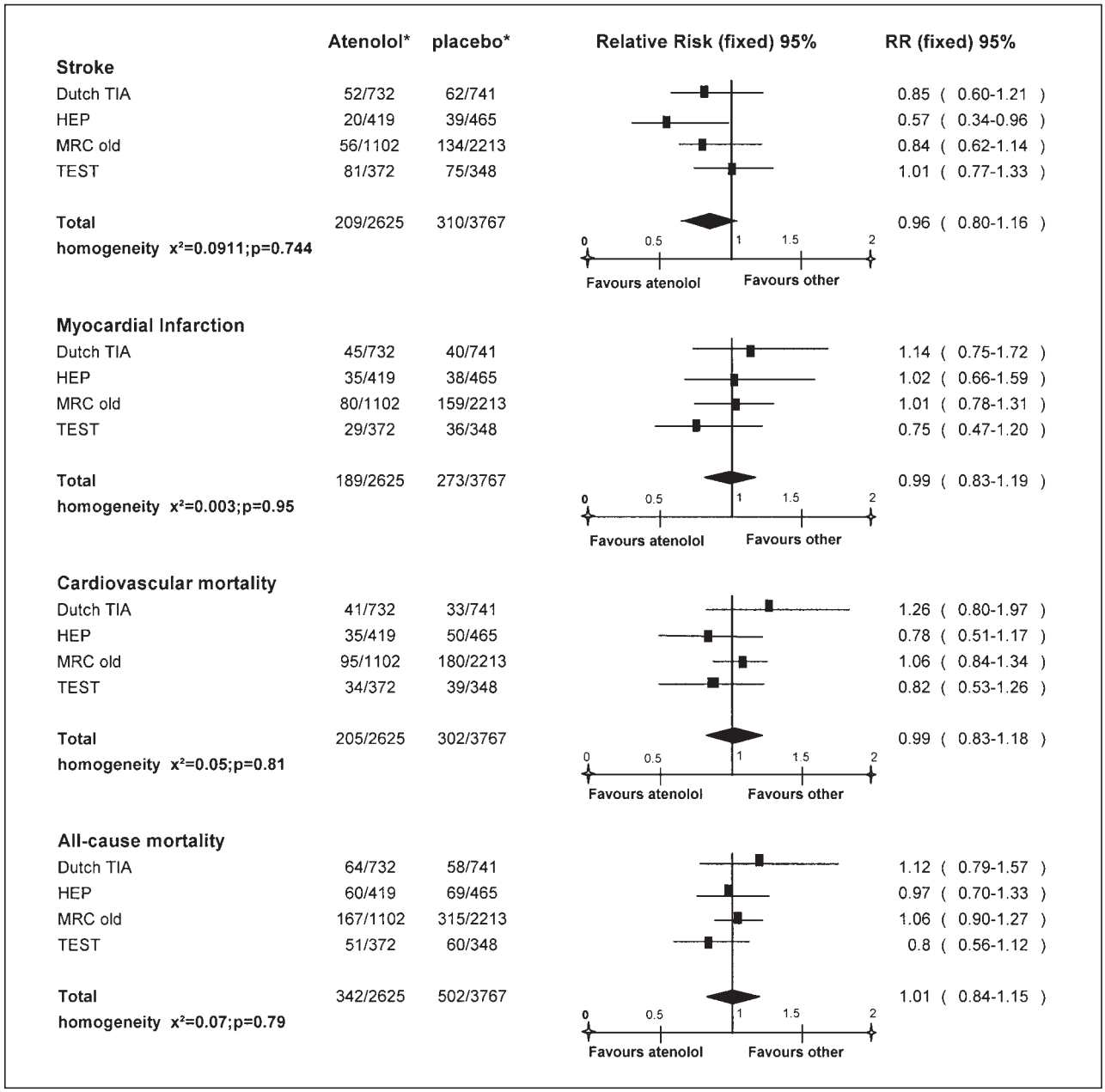

Figure 2. Outcome data for atenolol versus placebo.
*number of patients with events / total number of patients.

early morning rise of blood pressure, atenolol did not.[55] Neutel et al. have reported a similar lack of 24-hour effect with once-daily atenolol but a sustained effect with acebutolol.[56]

It is well-known that left ventricular hypertrophy is an independent cardiovascular risk factor in the general population, in essential and secondary hypertension, as well as in coronary heart disease.[57-60] Regression of left ventricular hypertrophy is significantly linked to central rather than brachial blood pressure.[61] A meta-analysis of 80 trials has shown that antihypertensive drug classes differ in their effects on left ventricular mass in hypertensive patients. Despite similar reduction in blood pressure, angiotensin-converting enzyme inhibitors, calcium channel blockers and angiotensin II receptor antagonists were significantly more effective in reducing left ventricular mass than beta-blockers.[62] This might be related to the smaller

effect of beta-blockers on central aortic blood pressure, which is the main haemodynamic determinant for the development of left ventricular hypertrophy.

Atenolol differs from other beta-blockers in its low lipophilic profile. Experimental studies have shown that the ability to prevent ventricular fibrillation depends on the amount of beta-blocker in the central nervous system.[63,64] The permeability of the hydrophilic atenolol into the central nervous system is very low. In addition, many antihypertensive drugs correct the remodelling and endothelial dysfunction of small arteries seen in hypertension, but this finding has not been seen for atenolol.[65-67] It has been reported that when patients who were controlled for a long period on atenolol were switched to an angiotensin II receptor antagonist, the arterial media/lumen diameter of resistance arteries decreased and endothelium-dependent relaxation increased.[68]

Finally, the adverse metabolic effects of atenolol could partially explain the less favourable outcome on cardiovascular disease. Glucose and lipid metabolism can be negatively affected during treatment with beta-blockers.[69] However, it is not clear whether this is also the case during long-term treatment with the low doses of these drugs recommended nowadays for the treatment of mild and moderate hypertension. It is noteworthy that the negative metabolic effects are more pronounced when beta-blockers are combined with thiazide diuretics.[70]

In conclusion, the present meta-analysis has shown that atenolol is not superior to placebo in the treatment of hypertensive patients. Moreover, in these patients the risk of stroke, cardiovascular and all-cause mortality is significantly higher with atenolol in comparison with other antihypertensive drugs. Therefore, atenolol should not be used as first choice drug in the treatment of patients with primary hypertension; however, atenolol should be used in hypertensive patients with compelling indications that require certain antihypertensive drug classes, such as coronary heart disease, post-myocardial infarction and heart failure.

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