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Baseline Heart Rate, Antihypertensive Treatment, and Prevention of Cardiovascular Outcomes in ASCOT (Anglo-Scandinavian Cardiac Outcomes Trial)

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Objectives The aim of this study was to evaluate the effect of baseline heart rate on the efficacy of atenolol-based compared with amlodipine-based therapy in patients with hypertension uncomplicated by coronary heart disease in the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm).

Background Heart rate is an established risk factor for cardiovascular events. Consequently, it is a widely held belief that beta-blockers should be prescribed for management of hypertension in patients with higher heart rates.

Methods Patients with atrial fibrillation or taking rate-limiting antihypertensive drugs at baseline were excluded. Primary analyses used Cox models to investigate the potential attenuation of the treatment effect with higher baseline heart rate on total cardiovascular events and procedures (TCVP) via introduction of an interaction term. Secondary analyses assessed coronary and total stroke outcomes.

Results Primary unadjusted analyses included 12,759 patients and 1,966 TCVP. At the final visit, mean heart rate reduction from baseline was 12.0 (SD 13.7) and 1.3 (SD 12.1) beats/min in atenolol- and amlodipine-based groups, respectively. There was a reduction in TCVP in those allocated amlodipine-based therapy compared with atenolol-based therapy (unadjusted hazard ratio: 0.81, $p < 0.001$). This benefit was unattenuated at higher heart rates (interaction p value = 0.81). Similar results were obtained for coronary and total stroke outcomes.

Conclusions There was no evidence that the superiority of amlodipine-based over atenolol-based therapy for patients with hypertension uncomplicated by coronary heart disease was attenuated with higher baseline heart rate. These data suggest that, in similar hypertensive populations without previous or current coronary artery disease, higher baseline heart rate is not an indication for preferential use of beta-blocker–based therapy. (J Am Coll Cardiol 2009;54:1154–61) © 2009 by the American College of Cardiology Foundation

Resting heart rate has been shown to be a significant and independent predictor of all-cause and cardiovascular mortality among men and women in the general population and in those with various cardiovascular conditions, including hypertension (1,2). In addition, post-exercise heart rate recovery (3) and heart rate variability are also associated with cardiovascular morbidity (4). In the post-myocardial infarction (MI) setting (5) and in heart failure (6), heart-rate reduction has been shown to be 1 of the important mechanisms whereby beta-blockers exert beneficial effects on cardiovascular morbidity and mortality. Consequently, heart rate is included in some risk assessment models for patients after acute coronary syndrome or post-MI (7,8), although most risk-assessment tools do not include pulse rate in the context of primary prevention (9,10). Nevertheless, most physicians believe that a high heart rate at rest is undesir-

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able, and at least some guidelines for hypertension management have recommended the use of beta-blockers as first-line therapy for those with "increased sympathetic tone" or a relative tachycardia (1,11–14). Hitherto no trial evidence is available to confirm or refute whether such an approach for patients with hypertension is preferable to the use of other agents that do not reduce the pulse rate. In the ASCOT-BPLA study (Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm), over 19,000 hypertensive patients without prior or current coronary artery disease were randomized to receive an amlodipine- or an atenolol-based regimen (15). The database for this trial therefore afforded the opportunity to evaluate whether the previously reported superior effects of the amlodipine-based regimen on cardiovascular events was attenuated among those with higher heart rates at baseline.

Methods

The design, conduct, and results of the ASCOT-BPLA study have been reported previously (15,16), and further details are available on the ASCOT website. Briefly, 19,257 patients were recruited between February 1998 and May 2000 mainly from family practices in the United Kingdom, Ireland, and the Nordic Countries. Patients were randomized to either atenolol ± bendroflumethiazide (atenolol-based) or amlodipine ± perindopril (amlodipine-based) antihypertensive treatment regimens. Because ASCOT was a 2 × 2 factorial study, 10,240 patients were also eligible to be randomized to the lipid-lowering arm of the study (ASCOT-LLA) in which atorvastatin 10 mg was compared with placebo (16,17).

Trial eligibility. Patients were eligible for the ASCOT-BPLA study if they had either untreated hypertension (systolic blood pressure [BP] ≥160 mm Hg and/or diastolic BP ≥100 mm Hg) or treated hypertension with systolic BP ≥140 mm Hg and/or diastolic BP ≥90 mm Hg and were age 40 to 79 years with at least 3 of the following other cardiovascular risk factors: male sex, age ≥55 years, microalbuminuria or proteinuria, smoking, total to high-density lipoprotein cholesterol ratio ≥6, family history of premature coronary heart disease (CHD), left ventricular hypertrophy, other specified abnormalities on electrocardiogram, type 2 diabetes mellitus, peripheral arterial disease, and previous stroke or transient ischemic attack.

Patients who had a previous history of MI, currently treated angina, a cerebrovascular event in the last 3 months, fasting triglyceride level >4.5 mmol/l, heart failure, uncontrolled arrhythmias, or any clinically important hematological or biochemical abnormality in routine screening were excluded from the trial.

Heart rate measurement. Heart rate and BP were measured at screening, baseline, and at every follow-up visit (6 weeks, 3 months, 6 months, and every 6 months thereafter) with a semi-automated device after 5 min rest in the sitting position. Heart rate and BP were measured 3 times at each visit, and the mean of the last 2 readings were used for analysis.

Abbreviations and Acronyms

BP = blood pressure
CHD = coronary heart disease
MI = myocardial infarction
TCVP = total cardiovascular events and procedures

Analysis population. Patients were excluded if they were recorded as taking a beta-blocker or any other rate-limiting antihypertensive drug at screening (or between screening and randomization if documented), to ensure that only patients with a baseline heart rate reading unaffected by pre-randomization antihypertensive treatment were included in the analysis population. For the majority of patients taking a calcium-channel blocker at screening, information on the specific type of drug was not available. These patients were included in the analysis population, because it was most likely that they were taking a dihydropyridine (which does not slow the heart rate) rather than verapamil or diltiazem (which do slow the heart rate). However, sensitivity analyses excluding calcium channel blockers of any type were also performed. Patients with known atrial fibrillation at baseline were excluded.

Statistical methods. Summary statistics of all baseline variables for the main analysis population were compared with those of the total ASCOT-BPLA population, by allocated treatment. All analyses of antihypertensive treatment groups were on an intention-to-treat basis.

Crude event rates were compared between treatment groups for categories of baseline heart rate, for the primary outcome "total cardiovascular event or procedure" (TCVP) and the secondary outcomes "nonfatal MI (including silent) or fatal CHD" (the ASCOT-BPLA primary end point), and "total stroke." Cox proportional hazards models were used to assess evidence for a baseline heart rate and treatment interaction with both unadjusted models and models with adjustment for all baseline predictors. Baseline heart rate was primarily modeled as a continuous variable but was also categorized into tertiles and into intervals of 10 beats/min.

For all 3 outcomes, baseline predictors of the outcome were initially identified via univariable Cox models. With a forward stepwise approach with baseline heart rate and treatment group (including the ASCOT-LLA treatment group) fixed in the models, preferred multivariable models were developed containing all predictors of the outcome. If 2 or more potential predictors were strongly related to each other, a choice was made about which to enter into the multivariable analysis on the basis of the comparative strength of the relationships and what was useful to adjust for on a clinical basis. An interaction between baseline heart rate and treatment group was then added to the models, and all baseline variables not currently in the models were reassessed as potential predictors.

The proportionality assumption of the Cox models was investigated with Schoenfeld residuals as well as interactions between baseline variables and follow-up time periods. The linearity of all continuous variables including heart rate was also investigated. Variables showing evidence of nonlinearity were categorized accordingly.

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Baseline creatinine, glucose, triglycerides, low-density lipoprotein cholesterol, body mass index, and weekly alcohol consumption variables had varying degrees of missing data (3%, 10%, 9%, 11%, <1%, and <1%, respectively). The final multivariable Cox models reported for each outcome exclude those patients with missing data for the included variables. However, analyses were repeated with multiple imputation methods to replace missing values in the main models.

A number of sensitivity analyses were performed mainly to assess the robustness of the results by rerunning the final multivariable models within chosen subsets of the analysis population, although it should be noted that for some analyses the number of patients and events included was markedly reduced. Sensitivity analyses were performed: 1) excluding patients taking calcium-channel blockers at screening; 2) excluding patients with prior stroke, transient ischemic attack, peripheral vascular disease, or other cardiovascular disease at baseline and then additionally excluding those with diabetes at baseline; and 3) stratifying by randomization to the statin or placebo arms of the trial.

All significance levels are 2-sided. Analyses were performed with the statistical software Stata version 10.0 (Stata Corp., College Station, Texas).

Results

Among 19,257 hypertensive patients randomized into ASCOT-BPLA, 12,759 were not taking a rate-limiting antihypertensive drug at baseline and were therefore eligible for the current analyses. The eligible subgroup were very similar to those in the trial overall in terms of demographic variables, inclusion criteria, biochemical measurements, BP levels, medical history, and other previous treatments (Table 1). Furthermore, those randomized to atenolol- or amlodipine-based treatment among the eligible subgroup did not differ importantly with regard to any of these baseline parameters. The small differences that were apparent (e.g., serum triglycerides and heart rate) reflect the omission of beta-blocker–treated patients in the analysis population. In summary, the population under investigation was largely male and white (77% and 95%, respectively) with a mean age of 63 years, among whom approximately one-quarter were diabetic and one-third smokers. Just over one-quarter were not taking antihypertensive medications at baseline, and mean BP levels were 165/95 mm Hg with a mean heart rate of 74 beats/min.

Baseline heart rates were higher among women than men, among smokers than nonsmokers, and among diabetic than nondiabetic subjects. Heart rates tended to fall with increasing age but increase with increasing body mass index, diastolic BP, reported alcohol intake, fasting plasma triglyceride levels, and fasting glucose levels (Online Table).

By the end of follow-up overall baseline heart rate had fallen by a mean of 12.0 (SD 13.7) and 1.3 (SD 12.1) beats/min among those randomized to atenolol- and amlodipine-based therapy, respectively. Atenolol allocation was associated with a fall in heart rate throughout the trial, irrespective of baseline heart rate, whereas among those allocated amlodipine, heart rates rose among those in the lowest tertile of baseline heart rates, fell among those in the highest baseline tertile, and remained mainly unchanged in the middle group.

With Cox regression, baseline heart rate did not significantly predict subsequent TCVP, nonfatal MI or fatal CHD, or total stroke outcomes in univariable (unadjusted) or multivariable (adjusted for all baseline predictors and excluding those with missing baseline values) analyses (Table 2). By contrast, allocation to amlodipine-based therapy was associated with large reductions in all 3 end points in univariable and multivariable analyses, although this was not statistically significant for coronary events.

There was no evidence that increasing baseline heart rate attenuated the benefit of amlodipine-based therapy relative to atenolol-based therapy for all 3 end points in univariable and multivariable analyses when treating baseline heart rate as a continuous variable (Table 2). Similarly, in alternative models with 5 categories of baseline heart rate at 10-beat/min intervals, there was no apparent attenuation of the superior impact of allocation to amlodipine-based as compared with atenolol-based therapy on crude event rates with higher baseline heart rates (Fig. 1). Moreover, the unadjusted hazard ratios of developing each of the 3 end points by allocated BP treatment were unaffected by baseline heart rate category (data not shown). When the data were fully adjusted for all baseline predictors and excluding all patients with any missing baseline values, the results were essentially unchanged (Fig. 2). Consistent results were obtained with categories on the basis of tertiles of baseline heart rate (data not shown). In addition, baseline heart rate showed no significant association with any of the 3 end points in univariable or multivariable analyses when each of the 2 BP-lowering treatment limbs was considered separately (Table 2).

Similar results to those presented were obtained when analyses were repeated with multiple imputation methods to replace missing baseline values in the main models. Results were also essentially unchanged in sensitivity analyses where all main models were rerun after excluding patients taking calcium channel blockers at screening. Similarly, findings did not alter in any important way in sensitivity analyses excluding patients with prior stroke, transient ischemic attack, peripheral vascular disease, or other cardiovascular disease at baseline or those analyses additionally removing patients with diabetes at baseline. Sensitivity analyses of the main results stratifying by randomization to statin or placebo arms of the trial gave no signal that results differed between these 2 groups.

Table 1 Baseline Characteristics for Main Analysis Population and Total ASCOT-BPLA Population by Allocated Antihypertensive Treatment Group

	Analysis Population (n = 12,759)		Total ASCOT-BPLA Population (n = 19,257)	
Baseline Variables	Atenolol (n = 6,361)	Amlodipine (n = 6,398)	Atenolol (n = 9,618)	Amlodipine (n = 9,639)
Statin trial, n (%)				
Yes: placebo	1,696 (27)	1,727 (27)	2,562 (27)	2,544 (26)
Yes: statin	1,712 (27)	1,740 (27)	2,570 (27)	2,564 (27)
No	2,953 (46)	2,931 (46)	4,486 (47)	4,531 (47)
Patient characteristics				
Heart rate, beats/min, mean (SD)	73.8 (12.1)	73.8 (12.1)	71.8 (12.6)	71.9 (12.7)
Age in yrs, mean (SD)	63.0 (8.6)	62.8 (8.6)	63.0 (8.5)	63.0 (8.5)
Male, n (%)	4,893 (77)	4,910 (77)	7361 (77)	7,381 (77)
Body mass index in kg/m^2, mean (SD)†	28.5 (4.4)	28.5 (4.5)	28.7 (4.5)	28.7 (4.5)
Current smoker, n (%)	2,156 (34)	2,212 (35)	3,109 (32)	3,168 (33)
Diabetic, n (%)	1,761 (28)	1,729 (27)	2,572 (27)	2,565 (27)
Systolic BP, mm Hg, mean (SD)	164.5 (17.5)	164.5 (17.6)	163.9 (18.0)	164.1 (18.1)
Diastolic BP, mm Hg, mean (SD)	94.8 (10.5)	95.2 (10.5)	94.5 (10.4)	94.8 (10.4)
Alcohol, U/week, mean (SD)†	7.9 (11.5)	8.0 (11.6)	7.9 (11.7)	8.0 (11.6)
Left ventricular hypertrophy, n (%)	1,306 (21)	1,347 (21)	2,076 (22)	2,091 (22)
Metabolic syndrome, n (%)	2,529 (40)	2,472 (39)	4,043 (42)	4,048 (42)
Ethnicity, n (%)				
White/Europid	6,041 (95)	6,065 (95)	9,170 (95)	9,187 (95)
African	178 (3)	168 (3)	240 (2)	223 (2)
Mixed/other/Oriental	62 (1)	69 (1)	94 (1)	97 (1)
South Asian	80 (1)	96 (2)	114 (1)	132 (1)
Medical history, n (%)				
Family coronary artery disease	1,755 (28)	1,817 (28)	2,629 (27)	2,655 (28)
Stroke/TIA	645 (10)	673 (11)	1,063 (11)	1,050 (11)
Vascular disease*	1,025 (16)	1,016 (16)	1,586 (16)	1,546 (16)
Other cardiovascular disease	315 (5)	319 (5)	486 (5)	533 (6)
Noncardiovascular concomitant disease	3,815 (60)	3,763 (59)	5,741 (60)	5,651 (59)
Biochemical results, mmol/l, mean (SD)				
HDL cholesterol	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)
Total cholesterol	5.9 (1.1)	5.9 (1.1)	5.9 (1.1)	5.9 (1.1)
Fasting triglycerides†	1.8 (1.0)	1.8 (1.0)	1.9 (1.0)	1.8 (1.0)
LDL cholesterol†	3.8 (1.0)	3.8 (1.0)	3.8 (1.0)	3.8 (1.0)
Fasting glucose†	6.3 (2.2)	6.2 (2.2)	6.2 (2.1)	6.2 (2.1)
Creatinine†	98.1 (16.8)	97.9 (16.9)	98.56 (16.8)	98.5 (16.8)
Baseline medical treatment, n (%)				
Aspirin	1,141 (18)	1,160 (18)	1,837 (19)	1,851 (19)
Lipid-lowering	625 (10)	669 (10)	1,004 (10)	1,046 (11)
At least 1 antihypertensive drug	4,578 (72)	4,566 (71)	7,793 (81)	7,798 (81)
Beta-blocker	—	—	3,072 (30)	3,086 (32)
Diuretic	1,652 (26)	1,699 (27)	2,764 (29)	2,726 (28)
Calcium-channel blocker	2,011 (32)	1,935 (30)	2,791 (29)	2,724 (28)
Angiotensin-converting enzyme inhibitor	1,903 (30)	1,983 (31)	2,437 (25)	2,535 (26)
Angiotensin receptor blocker	486 (8)	476 (7)	616 (6)	602 (6)
Alpha blocker	284 (4)	296 (5)	415 (4)	421 (4)
Other	44 (1)	45 (1)	125 (1)	132 (1)

*Stroke/transient ischemic attack (TIA) or peripheral vascular disease. †Missing values: for analysis population — body mass index = 2 (<1%); units of alcohol/week = 5 (<1%); fasting triglycerides = 1,210 (9%); low-density lipoprotein (LDL) cholesterol = 1,422 (11%); fasting glucose = 1,237 (10%); creatinine = 407 (3%).

ASCOT-BPLA = Anglo-Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm; BP = blood pressure; HDL = high-density lipoprotein.

Discussion

The presence of a rapid heart rate and hypertension has been suggested to be an indication for using beta-blockers as an initial antihypertensive therapy (1,11–14). However, before this analysis there were no data available from randomized controlled trials to assess the impact of this advice on patient outcomes (12). In this large substudy of the ASCOT study, as in the main study, amlodipine-based therapy was superior at reducing cardiovascular events

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Table 2 Cox Model Results Relating to Baseline Heart Rate and Allocated Treatment Group for All 3 Outcomes, Both Unadjusted and Adjusted for All Baseline Predictors

	Total CV Events and Procedures (n = 12,759, d = 1,966)*			Nonfatal MI and Fatal CHD (n = 12,759, d = 607)*			Total Stroke (n = 12,759, d = 490)*		
Models	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
Unadjusted									
Allocated treatment									
Amlodipine†	0.81	0.74–0.88	<0.001	0.88	0.75–1.03	0.11	0.74	0.62–0.88	0.001
Baseline heart rate (per 5 beats/min)									
Overall	0.99	0.97–1.01	0.43	1.03	0.99–1.06	0.10	1.01	0.97–1.04	0.70
Atenolol	0.99	0.97–1.02	0.69	1.03	0.98–1.07	0.24	1.01	0.97–1.06	0.60
Amlodipine	0.99	0.96–1.02	0.50	1.03	0.98–1.08	0.25	1.00	0.95–1.06	0.99
Interaction p value‡	—	—	0.81	—	—	0.98	—	—	0.73
Adjusted§									
Allocated treatment									
Amlodipine†	0.80	0.72–0.87	<0.001	0.86	0.73–1.02	0.09	0.75	0.62–0.91	0.003
Baseline heart rate (per 5 beats/min)									
Overall	1.00	0.98–1.02	0.69	1.02	0.98–1.06	0.27	1.02	0.98–1.06	0.43
Atenolol	1.00	0.98–1.03	0.81	1.02	0.97–1.07	0.45	1.03	0.98–1.08	0.31
Amlodipine	1.01	0.98–1.04	0.72	1.02	0.97–1.08	0.40	1.00	0.94–1.06	0.99
Interaction p value‡	—	—	0.91	—	—	0.91	—	—	0.51

*Due to missing values of some baseline variables, n = 11,520, d = 1,749; n = 11,165, d = 529; and n = 11,163, d = 419, for the adjusted models of the total cardiovascular events and procedures, myocardial infarction (MI) (including silent) and fatal coronary heart disease (CHD), and total stroke outcome models, respectively. †Atenolol is reference group. ‡p value for interaction between allocated treatment and baseline heart rate. §For each of the 3 outcomes, in addition to the heart rate and BPLA treatment group variables there was adjustment for: total cardiovascular events and procedures: lipid-lowering arm (LLA) treatment group, age, current smoker, previous vascular disease, sex, systolic blood pressure (BP), glucose, other cardiovascular disease, total cholesterol, HDL cholesterol, triglyceride, ethnicity, previous antihypertensive treatment, left ventricular hypertrophy, noncardiovascular concomitant disease, and previous aspirin therapy; MI (including silent) and fatal CHD: LLA treatment group, age, current smoker, previous vascular disease, sex, systolic BP, glucose, total cholesterol, HDL cholesterol, triglyceride, ethnicity, and creatinine; and total stroke: LLA treatment group, age, current smoker, previous stroke/TIA, systolic BP, glucose, other cardiovascular disease, previous antihypertensive treatment, creatinine, and alcohol.
HR = hazard ratio; d = number of events; other abbreviations as in Table 1.

compared with atenolol-based therapy. Atenolol-based therapy reduced heart rate more effectively than amlodipine at all baseline heart rates. Nevertheless, in both unadjusted and adjusted analysis, there was no tendency toward a reduction in the advantage of amlodipine- over atenolol-based therapy with higher baseline heart rates even in the highest categories of heart rate. Clearly, the study had reduced power to assess the impact of baseline heart rate on individual components of TCVP such as CHD and total stroke, but for these end points the results also showed no tendency for higher pulse rates to be associated with an attenuation of the superiority of amlodipine-based therapy. Consequently, our analysis does not support the specific use of atenolol as initial antihypertensive therapy in those with or without a high baseline heart rate, and more generally it seems reasonable to conclude, pending contradictory evidence, that a higher heart rate should not be used as the basis for selecting a beta-blocker in hypertensive patients unless specific indications such as heart failure or ischemic heart disease apply.

Study limitations. First, the study hypothesis was developed after the conduct of the trial. Nevertheless, in the multiple analyses with different end points we found no evidence of an interaction between therapies based on atenolol or amlodipine and heart rate, and furthermore, there was no evidence from adjusted analyses that age or sex influenced the lack of effect of heart rate on the outcomes of atenolol- or amlodipine-based therapy. Second, the analyses involved a subsample (albeit large) of the overall trial population, due to our exclusion of patients treated with heart rate-lowering drugs before the start of the trial. Although this exclusion criterion was necessary to assess "true" baseline heart rate, it is theoretically possible that it might also have created a bias by excluding patients with more rapid baseline heart rates who might have benefited more from rate-limiting therapy. However, among the total ASCOT population, which included patients taking pre-existing heart rate-lowering therapy, the superiority of amlodipine-based therapy was not diluted compared with the benefits shown in these analyses (15). Third, there were only approximately 300 patients in the ASCOT study with baseline heart rates of over 100 beats/min, which limited our power to evaluate this group. However, approximately 1,100 patients had a baseline heart rate of over 90 beats/min, and no signal of an attenuated differential treatment effect was apparent in this group (Fig. 2). It is possible that some with a very rapid heart rate (e.g., those with a heart rate significantly >100 beats/min) might derive specific advantages from beta-blocker–based therapy. Finally, it is possible that heart rate at baseline might not truly reflect the usual heart rate for an individual entering the trial; however, heart rates at multiple visits before randomization were unfortunately not available in the ASCOT dataset to allow an evaluation of this potential shortcoming.

Baseline heart rate has been reported as a significant predictor of various cardiovascular outcomes in some but not all studies (1,2,18). In the ASCOT study, baseline heart rate did predict all-cause, noncardiovascular, and cardiovas-

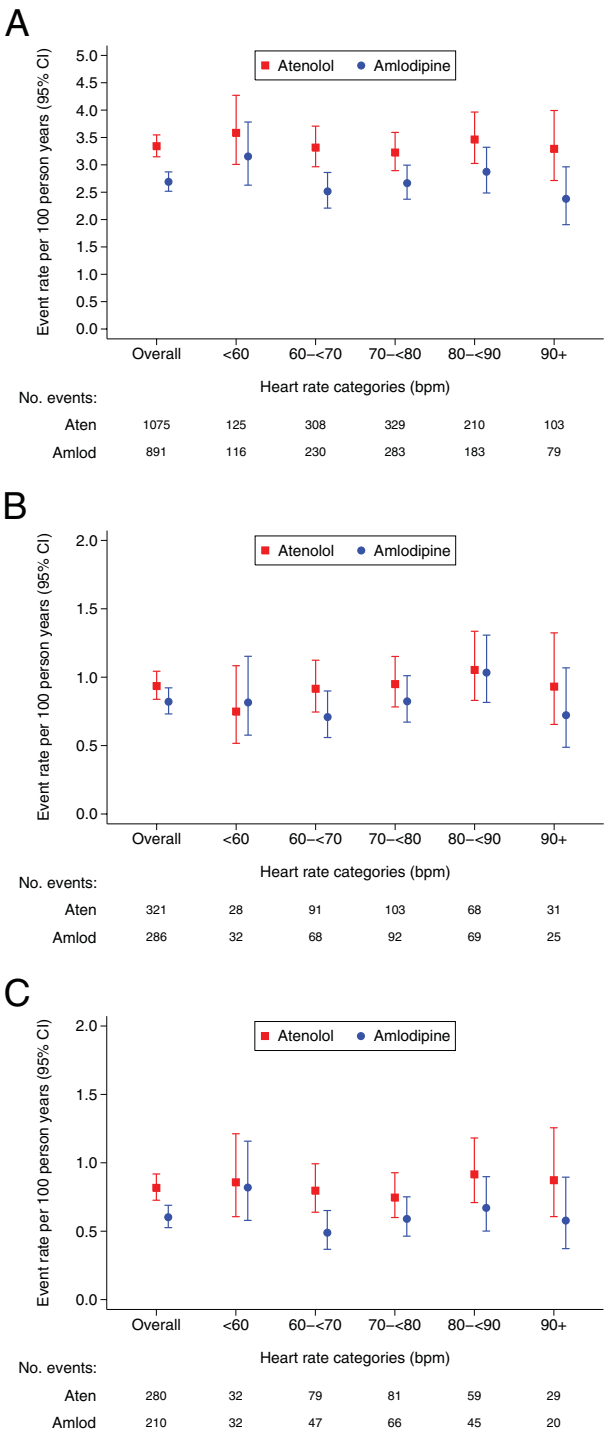

Figure 1 **Crude Event Rates by Allocated Treatment Group and Baseline Heart Rate Group**

Crude event rates/100 person-years and 95% confidence intervals (CIs) (n = 12,759): **(A)** total cardiovascular events and procedures (1,966 events); **(B)** nonfatal myocardial infarction (including silent) and fatal coronary heart disease (607 events); **(C)** total stroke (490 events). bpm = beats/min.

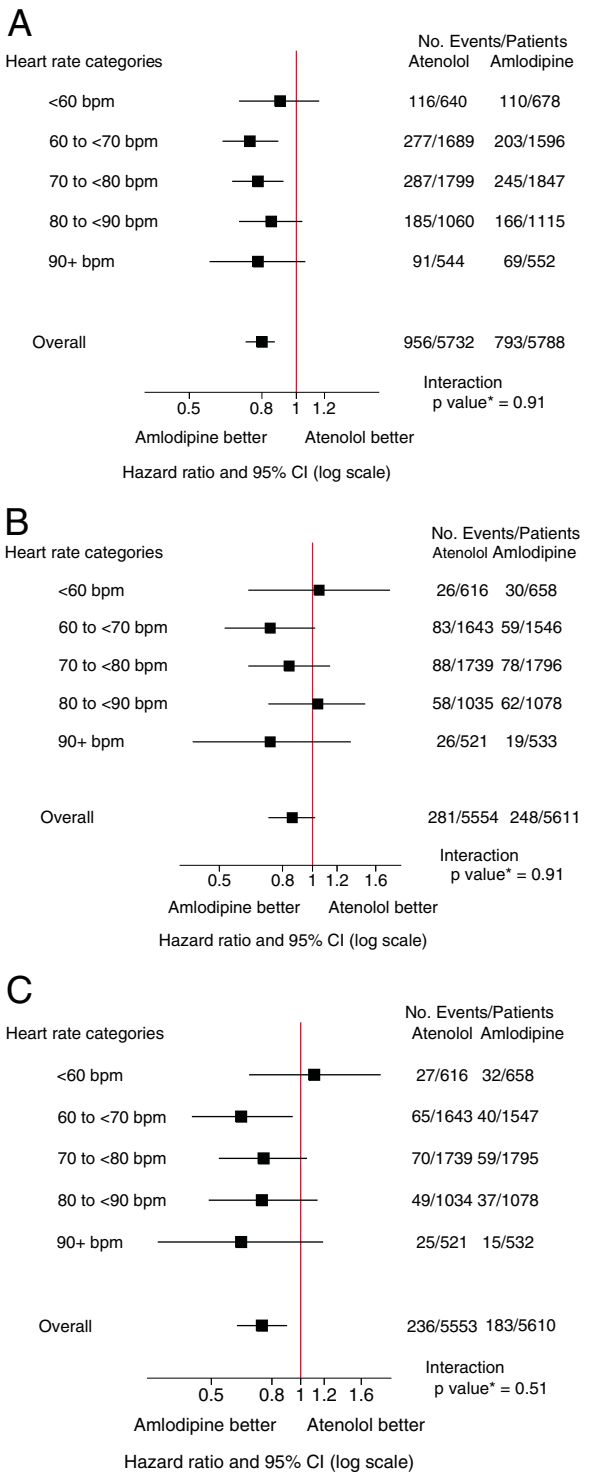

Figure 2 **Hazard Ratios for Allocated Antihypertensive Treatment by Baseline Heart Rate Group**

Hazard ratios and 95% CIs after adjusting for all baseline predictors and excluding patients with missing baseline values: **(A)** total cardiovascular events and procedures outcome; **(B)** nonfatal myocardial infarction (including silent) and fatal coronary heart disease outcome; **(C)** total stroke outcome. *Interaction p value is for interaction between continuous heart rate and allocated treatment group. Abbreviations as in Figure 1.

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cular mortality but not nonfatal cardiovascular events (data not shown). Neither baseline nor attained heart rate at the 6-week interval in this subpopulation of the ASCOT study was associated with the TCVP or total stroke outcomes after multivariable adjustment, but there was some suggestion that heart rate at 6 weeks was associated with the nonfatal MI and fatal CHD outcome (data not shown). Why heart rate, either in the whole population or within each of the 2 BP-lowering treatment groups, was not consistently associated with all cardiovascular events in the ASCOT study is not clear, but it is possible that the impact of heart rate was obscured by more critical effects on cardiovascular outcomes such as large and rapid BP lowering and large changes in lipid profiles (15,17).

The current findings in the ASCOT study might well only relate to patients with hypertension uncomplicated by CHD. Beta-blocker therapy remains the initial therapeutic choice for the control of symptoms of ischemic heart disease, and to reduce mortality in patients who have had an MI and for those who have heart failure, beta-blockers are a critically useful add-on therapy. Indeed, in the setting of heart failure and MI, a rapid baseline heart rate and greater decline in heart rate are both associated with greater benefits from beta-blockade (1,12). It is possible that the reduction in myocardial oxygen consumption or antiarrhythmic properties of beta-blockers play a more substantive role in determining outcomes in these situations than in patients with hypertension. However, an analysis of the effect of heart rate in patients with ischemic heart disease and hypertension who were randomized to receive atenolol or verapamil in the INVEST (International Verapamil-Trandolapril Study) was recently reported (19). Although both baseline and on-treatment heart rate predicted cardiovascular outcomes in this high-risk population, the greater reduction in heart rate with atenolol compared with verapamil did not translate into fewer cardiovascular events. Hence, on the basis of these results, the superiority of lowering heart rate pharmacologically with a beta-blocker in those with hypertension and stable ischemic heart disease has not been demonstrated.

Conclusions

These analyses provide no evidence that atenolol-based therapy is superior to amlodipine-based therapy for patients with hypertension uncomplicated by CHD across the wide range of baseline heart rates observed in the ASCOT database. Pending further information—which could perhaps be gleaned from other studies, such as the LIFE (Losartan Intervention For Endpoint reduction in Hypertension) study (20)—beta-blocker–based therapies are not appropriate to select as initial therapy for hypertension on the basis of a higher heart rate unless congestive heart failure and/or symptomatic ischemic heart disease coexist.

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Key Words: beta-blockers ■ cardiovascular risk ■ heart rate ■ hypertension.

APPENDIX

For the supplementary table showing the mean baseline heart rate (and standard deviation) for various categorizations of baseline variables, by allocated antihypertensive treatment group, please see the online version of this article.