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Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the INternational VErapamil-SR/trandolapril STudy (INVEST)

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Aim To determine the relationship between resting heart rate (RHR) and adverse outcomes in coronary artery disease (CAD) patients treated for hypertension with different RHR-lowering strategies.

Methods and results Time to adverse outcomes (death, non-fatal myocardial infarction, or non-fatal-stroke) and predictive values of baseline and follow-up RHR were assessed in INternational VErapamil-SR/trandolapril STudy (INVEST) patients randomized to either a verapamil-SR (Ve) or atenolol (At)-based strategy. Higher baseline and follow-up RHR were associated with increased adverse outcome risks, with a linear relationship for baseline RHR and J-shaped relationship for follow-up RHR. Although follow-up RHR was independently associated with adverse outcomes, it added less excess risk than baseline conditions such as heart failure and diabetes. The At strategy reduced RHR more than Ve (at 24 months, 69.2 vs. 72.8 beats/min; $P < 0.001$), yet adverse outcomes were similar [Ve 9.67% (rate 35/1000 patient-years) vs. At 9.88% (rate 36/1000 patient-years, confidence interval 0.90–1.06, $P = 0.62$)]. For the same RHR, men had a higher risk than women.

Conclusion Among CAD patients with hypertension, RHR predicts adverse outcomes, and on-treatment RHR is more predictive than baseline RHR. A Ve strategy is less effective than an At strategy for lowering RHR but has a similar effect on adverse outcomes.

Keywords Coronary artery disease • Atenolol • Resting heart rate • Adverse outcomes • INVEST • Verapamil-SR

Introduction

The number of heartbeats in a lifetime is relatively constant across species with an inverse semi-logarithmic relationship between resting heart rate (RHR) and life expectancy.[1,2] In the general population, RHR is a strong correlate of blood pressure (BP) and mortality.[3–10] Among factors influencing RHR, the sympathetic nervous system (SNS) regulates both RHR and BP minute-by-minute as well as long term.[11] An increase in RHR reflects decreased parasympathetic tone and/or increased sympathetic tone. RHR correlates with coronary artery disease (CAD)[10,12–18] and a gender-related difference in this association, as well as with BP, has been suggested.[10,17,19]

In CAD patients, therapies that decrease RHR appear more beneficial than those that increase RHR.[1,20] RHR reduction, studied mostly from β-blocker trials of acute myocardial infarction (MI) or heart failure (HF), is associated with improved outcomes.[1,20] Favourable effects have also been suggested for non-dihydropyridine calcium antagonists via effects on the SNS and RHR.[20] Yet cardiac-slowing properties of antihypertensive drugs and associated effects on outcomes have not been studied in

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randomized trials in stable CAD or hypertension.[21] The general paucity of information on RHR and effects of cardiac-slowing drugs on outcomes perhaps explains why, despite the simplicity of measurement, physicians tend to ignore the prognostic information associated with RHR.

The aim of this study was to determine the relationships between RHR, both at baseline and follow-up, and adverse outcomes in CAD patients with hypertension. We used the INternational VErapamil-SR/trandolapril STudy (INVEST) database which included treatment with either a β-blocker or heart-rate-slowing calcium antagonist strategy and follow-up where BP was <140/90 mmHg in >70% of the patients. Additionally, sufficient numbers of diabetes, prior MI, and female patients were present to examine the relationships between RHR and outcomes in these subgroups.

Methods

The design of the INVEST, a multinational, randomized study conducted according to the principles of the Declaration of Helsinki, has been described in detail previously.[22] Local ethics committees approved the protocol, and written informed consent was obtained from all subjects. Briefly, BP control and adverse outcomes using either a verapamil-SR-based (Ve) or an atenolol-based (At) treatment strategy were evaluated in hypertensive patients ($n = 22\,576$) with clinically stable CAD. Treatment goals were BP <140/90 or <130/85 mmHg for patients with diabetes or renal impairment, respectively.[23] The primary outcome, hereafter termed adverse outcome, was the first occurrence of all-cause death, non-fatal MI, or non-fatal stroke. Standard-of-care non-pharmacological recommendations based on the Sixth Report of the Joint National Committee (JNC VI) Guidelines[23] and secondary prevention according to the National Cholesterol Education Program[24] were provided online in printable format that could be given to patients. At each visit, the protocol required a clinical evaluation and exam when BP was measured according to JNC VI recommendations[23] and RHR was measured at the same time and also in duplicate. These measurements were entered to INVEST online data entry forms which averaged the RHR and BP values and electronically transmitted the information to the Data Coordinating Center.

Participants received either 240 mg/day Ve SR or 50 mg/day At, with titration to maximum doses to achieve target BPs. If the BP goal was not achieved, trandolapril and hydrochlorothiazide were recommended. ACE inhibition (trandolapril) was also recommended for participants with diabetes, HF, or renal impairment.[23] The protocol recommended that the follow-up clinic visits be scheduled such that BP would be recorded at approximately the same time of the day and by the same person for each individual subject. Visits were scheduled every 6 weeks for the first 6 months and every 6 months thereafter and follow-up averaged 2.7 years. A total of 568 patients did not return for a final visit and were not found in death searches.[25]

From the overall cohort, 384 patients with an electronic pacemaker were excluded, resulting in 22 192 patients for this analysis. Continuous variables and categorical variables were summarized as means ± SD where appropriate and compared by *t* test and by χ^2 test, respectively. Median doses were determined for the drug doses used within the randomized treatment strategies. A *P*-value of ≤0.05 (two-sided) was considered significant and because all analyses were exploratory, no adjustments were made for multiplicity. Hazard ratios and 95% confidence intervals (CIs) were determined. Stepwise Cox proportional hazards (PH) modelling was used to compare time to adverse outcomes between randomized treatment strategies and to assess the importance of baseline RHR as a predictive variable. Randomized treatment strategy, pre-specified baseline covariates (age, gender, race, prior MI, prior HF), and baseline RHR were forced terms in the model; other baseline covariates were selected if $P \leq 0.1$.

Mean follow-up RHR was also calculated for each patient using all follow-up visit values to the date of adverse outcomes, censoring, or study completion. Baseline values were substituted for patients ($n = 1115$) with no follow-up RHR data (e.g. either lost to follow-up as noted above or dead). A separate exploratory analysis combining patients for treatment strategies using a stepwise Cox PH model with linear and quadratic terms for mean follow-up RHR was performed to estimate hazard ratio relative to 75 b.p.m. This was repeated for subgroups with diabetes, prior MI, and also for gender. The assumption of PH was tested using time-dependent covariates. For covariates not meeting the PH assumption, the obtained RHR (95% CIs) reflected an average effect over the range of time observed in the data set. Statistical analysis was performed using SAS software.

Results

Baseline characteristics (*Table 1*) were generally well balanced between treatment strategies and similar to the overall INVEST population described previously.[25] More patients with prior stroke/transient ischaemic attack (TIA) were assigned the Ve strategy. At 24 months follow-up, RHR was reduced to a greater extent in the At group (At 69.2 vs. Ve 72.8 b.p.m.; $P < 0.001$), however, adverse outcomes did not differ significantly [Ve 9.67% (rate 35 per 1000 patient-years) vs. At 9.88% (rate 36 per 1000 patient-years) and $P = 0.62$].

Impact of resting heart rate at baseline

The frequency distribution of baseline RHR appears in the bottom of *Figure 1*. Mean RHR was 75.7 ± 9.6 b.p.m. in both strategies, as the majority (80.1%) ranged from 60 to 85 b.p.m., and few patients had RHR >100 b.p.m. [217 patients (1.0%)] or RHR ≤60 b.p.m. [1266 patients (5.7%)]. Elevated baseline RHR was associated with increased incidence of adverse outcomes (*Figure 1*, top) with a ∼two-fold increase among patients with RHR >100 b.p.m. (vs. those with ≤100 b.p.m.). For those with RHR <100 but >55 b.p.m., this incidence (∼10% mean) was similar and there were no significant differences by strategy across the entire RHR range. A linear relationship was observed between baseline RHR and risk for adverse outcomes (data not shown) as a 5-b.p.m. increment was associated with a 6% excess risk (stepwise Cox PH model, *Figure 2*). Results were similar in the unadjusted model for baseline RHR per 5-b.p.m. increments [hazard ratio 1.05 (95% CI 1.03–1.07), $P < 0.001$].

Impact of resting heart rate during follow-up

In the overall study population, mean follow-up RHR was strongly associated with risk for adverse outcomes and a J-shaped relationship was observed (*Figure 3*). A J-shaped relationship was also observed for time-dependent mean follow-up RHR and risk (data not shown). Increases in mean follow-up RHR from 70 to 80 b.p.m. were associated with a 31% excess risk

Table 1 Baseline demographics of patients without a pacemaker at baseline

	All patients (n = 22 192)	Verapamil-SR (n = 11 094)	Atenolol (n = 11 098)	P-value
SBP, mean ± SD (mmHg)	150.9 ± 19.5	150.8 ± 19.5	151.0 ± 19.6	0.61
DBP, mean ± SD (mmHg)	87.3 ± 11.9	87.2 ± 11.9	87.3 ± 11.9	0.84
Heart rate, mean ± SD (b.p.m.)	75.7 ± 9.6	75.7 ± 9.6	75.7 ± 9.5	0.68
Age, mean ± SD (year)	65.9 ± 9.7	65.8 ± 9.7	66.0 ± 9.7	0.33
Female	11592 (52.2%)	5768 (52.0%)	5824 (52.5%)	0.47
Caucasian	10664 (48.1%)	5349 (48.2%)	5315 (47.9%)	0.55
Prior myocardial infarction	7054 (31.8%)	3546 (32.0%)	3508 (31.6%)	0.57
Arrhythmias	1472 (6.6%)	747 (6.7%)	725 (6.5%)	0.55
Angina pectoris	14855 (66.9%)	7382 (66.5%)	7473 (67.3%)	0.21
Heart failure (Class I-III)	1182 (5.3%)	587 (5.3%)	595 (5.4%)	0.82
Coronary revascularization	5989 (27.0%)	2999 (27.0%)	2990 (26.9%)	0.88
Stroke	1120 (5.0%)	578 (5.2%)	542 (4.9%)	0.27
Stroke/TIA	1570 (7.1%)	829 (7.5%)	741 (6.7%)	0.02
Diabetes	6294 (28.4%)	3116 (28.1%)	3178 (28.6%)	0.36
Renal impairment	405 (1.8%)	207 (1.9%)	198 (1.8%)	0.65
Smoking (ever)	10282 (46.3%)	5167 (46.6%)	5115 (46.1%)	0.47

SBP, systolic blood pressure; SD, standard deviation; DBP, diastolic blood pressure; b.p.m., beats per minute; MI, myocardial infarction; TIA, transient ischaemic attack.

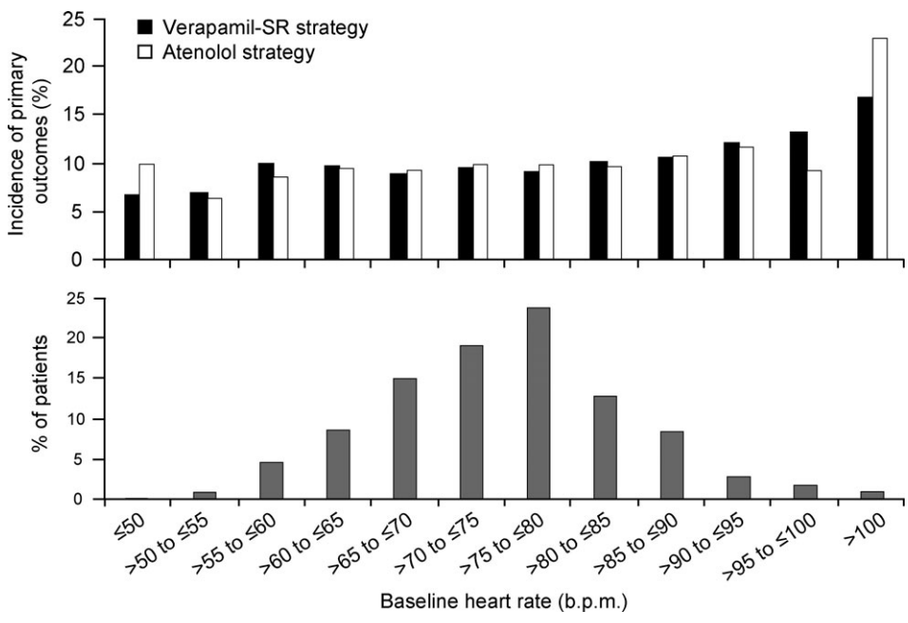

Figure 1 Top panel: incidence of adverse outcomes (time to first event of all-cause death, non-fatal myocardial infarction, or non-fatal stroke) among randomized patients without an electronic pacemaker for each treatment strategy by resting heart rate at baseline. Bottom panel: distribution of patients by baseline resting heart rate

for adverse outcomes. There was an association between baseline and follow-up RHR (correlation coefficient 0.42; $P < 0.001$), however baseline RHR was not statistically significant when tested in the same Cox PH model as follow-up RHR. For patients with baseline RHR >85 b.p.m. (3152 patients with 364 events), the relationship between follow-up RHR and risk was J-shaped. Among patients with baseline RHR ≤60 b.p.m. (1266 patients with 112 events), the relationship between follow-up RHR and risk was neither linear nor quadratic, perhaps because of the small number of events. But among patients with baseline RHR >85 b.p.m., the relationship between follow-up RHR and risk was no longer J-shaped in the two treatment strategies, again possibly because of the smaller sample sizes.

Baseline covariate	*n*/*N*	Event rate	HR (95% CI)	*P*-Value
Heart failure (class I-III)	274/1182	23.18%	1.91 (1.67–2.18)	<0.0001
Diabetes	882/6294	14.01%	1.78 (1.63–1.95)	<0.0001
Age (10 year increments)			1.64 (1.56–1.72)	<0.0001
US residency	1908/16807	11.35%	1.64 (1.43–1.87)	<0.0001
Renal impairment	108/405	26.67%	1.57 (1.29–1.92)	<0.0001
Smoker	1198/10282	11.65%	1.41 (1.29–1.55)	<0.0001
Prior stroke/TIA	299/1570	19.04%	1.41 (1.24–1.60)	<0.0001
Prior myocardial infarction	959/7054	13.60%	1.34 (1.22–1.46)	<0.0001
Peripheral vascular disease	412/2617	15.74%	1.25 (1.12–1.40)	<0.0001
Coronary revascularization	827/5989	13.81%	1.17 (1.06–1.29)	0.001
Arrhythmia	220/1472	14.95%	1.16 (1.01–1.34)	0.04
Gender (male vs. female)	1153/10600	10.88%	1.10 (1.01–1.21)	0.03
Heart rate (5 b.p.m. increments)			1.06 (1.04–1.08)	<0.0001
Strategy: verapamil-SR (vs. atenolol)	1073/11094	9.67%	0.97 (0.89–1.05)	0.42

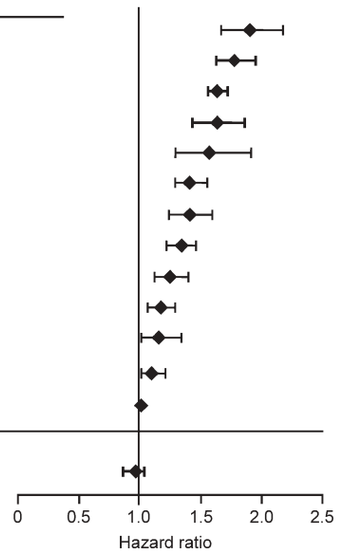

Figure 2 Conditions present at baseline that were associated with risk for adverse outcomes from a stepwise Cox proportional hazards model; *n*, number of patients with adverse outcome; *N*, number patients with baseline condition; event rate, adverse outcome incidence; HR, hazard ratio; CI, confidence interval; TIA, transient ischaemic attack; b.p.m., beats per minute; strategy, randomized treatment strategy

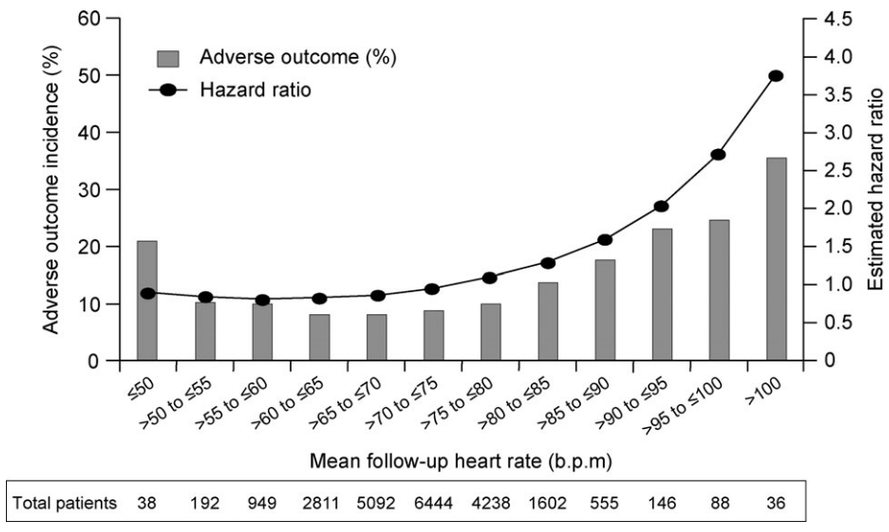

Figure 3 Relationship between follow-up resting heart rate for all patients and incidence of adverse outcomes (left axis, bars) and risk (right axis –●–, hazard ratio) derived from a stepwise Cox proportional hazards model. Among all patients, the nadir for follow-up resting heart rate was 59 b.p.m

Impact of study medications and baseline conditions relative to baseline and follow-up resting heart rate

The relationship between follow-up RHR and risk was J-shaped within both treatment strategies with a nadir at 59 b.p.m. for all patients as the nadir for the At strategy was lower (51 b.p.m.) vs. the Ve strategy (62 b.p.m.). At 24 months, for the Ve strategy, median doses of study medications were the same within the three groups of baseline and follow-up RHR (≤60, >60 to ≤85, and >85 b.p.m.): verapamil-SR 240 mg/day, trandolapril 4 mg/day, and HCTZ 25 mg/day. For the At strategy, however, median

atenolol dose was less in the lowest RHR group (≤60 b.p.m.) of baseline and follow-up RHR (50 mg/day) compared with the other two RHR groups (100 mg/day for each).

Similar J-shaped associations between mean follow-up RHR and risk were observed for patients with diabetes (*Figure 4*) as well as those with history of MI (*Figure 5*), with nadirs of 61 and 64 b.p.m., respectively. There was no difference between treatment strategies in follow-up RHR or adverse outcomes for these prior MI (*Table 2*) or diabetes (not shown) subgroups.

At baseline in the overall population, women ($n = 11\,592$) had a significantly higher mean RHR (76.2 ± 9.4 vs. 75.2 ± 9.7 b.p.m.; $P < 0.001$) than men ($n = 10\,600$). The same pattern in baseline RHR was found in those with prior MI (2697 women vs. 4357 men, 76.6 ± 9.8 vs. 75.0 ± 9.7 b.p.m.) and diabetes (3406 women vs. 2888 men; 77.3 ± 9.5 vs. 76.3 ± 9.6 b.p.m.). Mean baseline RHR was higher for women with, than for women without, diabetes (77.3 ± 9.5 vs. 75.7 ± 9.3 b.p.m.; $P < 0.001$).

Overall, women had significantly higher mean follow-up RHR against men (72.4 ± 7.2 vs. 70.9 ± 7.6 b.p.m.; $P < 0.001$); this was also true for subgroups with diabetes or prior MI and within treatment strategies. Mean follow-up RHR was significantly greater in the Ve strategy than in the At strategy for women (74.2 ± 6.6 vs. 70.6 ± 7.2 b.p.m.; $P < 0.001$) and for men (73.0 ± 6.8 vs. 68.9 ± 7.8 b.p.m.; $P < 0.001$).

Even though RHR was higher in women than in men, men had a greater risk of adverse outcomes (e.g. 10% excess risk; *Figure 2*). When adjusted for baseline RHR, the hazard ratio for men vs. women was 1.10 (95% CI 1.01–1.21; $P = 0.03$), whereas that for baseline RHR (5 b.p.m. increments) was 1.06 (95% CI 1.04–1.08; $P < 0.0001$; *Figure 2*). When adjusted for mean follow-up RHR, the hazard ratio for men vs. women was 1.12 (95%CI 1.02–1.23; $P < 0.001$), whereas that for follow-up RHR was 0.9084 (95% CI 0.8716–0.9467) for the linear term and 1.0008 (95% CI 1.0006–1.0011), with $P < 0.0001$ for both terms. The interaction of gender with RHR, either baseline ($P = 0.24$) or follow-up ($P = 0.79$ for the linear term and 0.95 for the quadratic term), was not statistically significant. The relationship between mean follow-up RHR and adverse outcomes was J-shaped for both men and women in two separate Cox PH models, with nadirs of 57 and 64 b.p.m., respectively.

Discussion

We investigated associations between baseline and follow-up RHR and adverse outcomes in elderly hypertensive patients with chronic CAD using the INVEST population. We found both RHR variables were associated with adverse outcomes with a linear relationship for baseline RHR and a J-shaped relationship for follow-up RHR. The novelty of our investigation is that the results were obtained in a population of treated patients with excellent BP control and also that follow-up RHR, using two different RHR-lowering treatment strategies, was tested as a predictor of adverse outcomes. Most studies on the clinical role of RHR have been carried out in untreated and different populations and in the limited data available (e.g. Syst-Eur study)[18] no relationship of RHR with outcome was found with treatment.

Our findings support and extend previous epidemiological and clinical studies, showing that increased RHR is associated with increased risk in patients with isolated systolic hypertension (ISH),[10] acute coronary syndromes,[26–28] and HF.[29,30] The increased risk that we observed was at an RHR as low as 75 b.p.m., well below the definition of tachycardia. Consistency of this observation across different risk levels suggests that increased RHR is a marker of additional risk. In our treated hypertensive CAD patients, elevated baseline and follow-up RHR were associated with an increasing risk for adverse outcomes consistent with findings from untreated elderly patients in the Syst-Eur trial[18] and patients with CAD and hypertension in the Coronary Artery

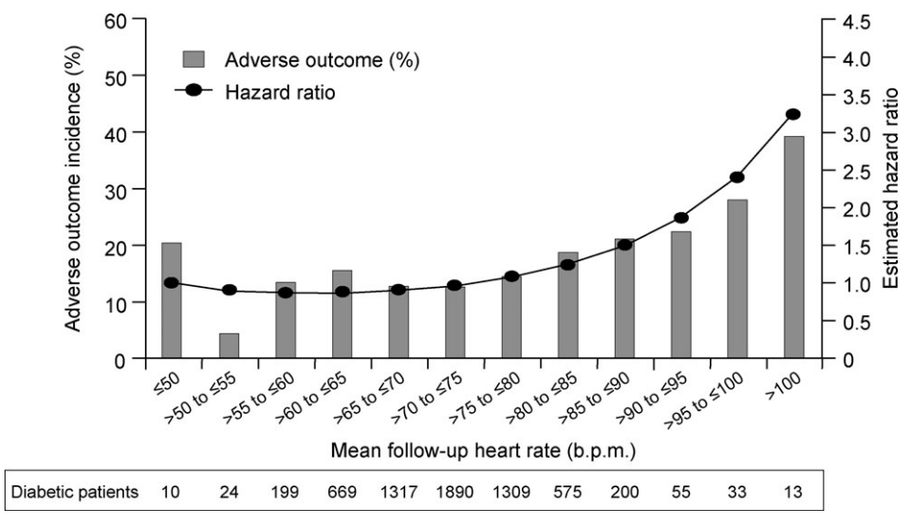

Figure 4 Relationship between follow-up resting heart rate among patients with diabetes and incidence of adverse outcomes (left axis, bars) and risk (right axis –●–, hazard ratio) derived from a stepwise Cox proportional hazards model

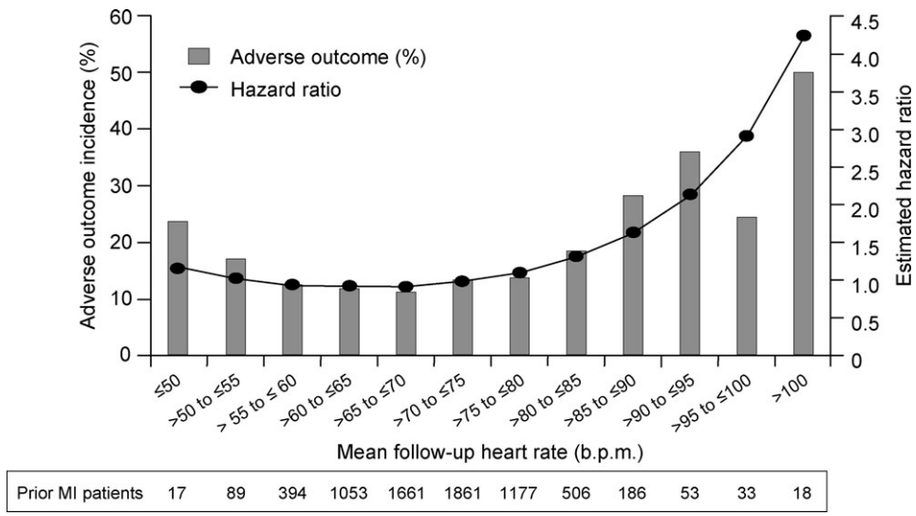

Figure 5 Relationship between follow-up resting heart rate among patients with prior myocardial infarction and incidence of adverse outcomes (left axis, bars) and risk (right axis -●-, hazard ratio) derived from a stepwise Cox proportional hazards model. MI, myocardial infarction

Table 2 Summary of outcomes in subjects with or without prior myocardial infarction and without a pacemaker at baseline

	Verapamil-SR strategy	Atenolol strategy	Hazard ratio (95% CI)	*P*-value
Prior MI				
n	3546	3508	NA	NA
Adverse outcome	467 (13.2%)	492 (14.0%)	0.93 (0.82−1.05)	0.24
Death	372 (10.5%)	366 (10.4%)	1.00 (0.86−1.15)	0.99
Non-fatal MI	67 (1.9%)	79 (2.3%)	0.83 (0.60−1.15)	0.27
Non-fatal stroke	50 (1.4%)	67 (1.9%)	0.73 (0.51−1.06)	0.10
No prior MI				
n	7548	7590	NA	NA
Adverse outcome	606 (8.0%)	604 (8.0%)	1.02 (0.91−1.14)	0.80
Death	463 (6.1%)	477 (6.3%)	0.98 (0.86−1.12)	0.78
Non-fatal MI	77 (1.0%)	74 (1.0%)	1.05 (0.76−1.45)	0.75
Non-fatal stroke	78 (1.0%)	75 (1.0%)	1.05 (0.77−1.44)	0.76

MI, myocardial infarction; NA, not applicable.

Surgery Study (CASS) registry.[31] These earlier studies suggested that RHR >75 and >77 b.p.m., respectively, were associated with increased risk of all-cause death[18,31] and >83 b.p.m. for cardiovascular death.[31] In our study, the association with increased risk is apparent with mean follow-up RHR >75 b.p.m. within both treatment strategies (*Figure 3*), whereas in the adjusted follow-up RHR model the nadir was 59 b.p.m.

Reports are conflicting as to whether the direct relationships between RHR and cardiovascular death or all-cause death are linear across the RHR range, or if risk becomes also increased at relatively low RHR (i.e. J-shaped).[16,18,26,27,31,32] Generally, studies of high-risk patients (e.g. with comorbidities such as ISH, unstable angina/non-ST-elevation MI) and men after acute MI have suggested a J-shaped relationship between RHR and all-cause death.[18,26,27] In support of these suggestions, the J-curve relationship between risk of adverse outcomes and mean follow-up RHR that we observed is slightly more pronounced in the diabetes (*Figure 4*) and prior MI (*Figure 5*) subgroups. It is unclear whether this increased risk at lower RHR may be directly related to underlying CAD severity or associated with unrecognized factors related to CAD. On the other hand, it should be pointed out that the upturn in the relationship was due to a small number of subjects (and events) in the lower RHR groups and that the upturn is more evident in the subgroup with prior MI. The linear relationship

between risk of adverse outcomes and baseline RHR observed here is consistent with recent findings from other patients with CAD.[31] However, in our analysis baseline RHR was not a significant predictor of adverse outcomes when included in the same model with mean follow-up RHR, suggesting that on treatment RHR contributes more information to the prediction of adverse outcomes. This has relevance to the report from the Syst-Eur trial,[18] where on treatment RHR was not associated with adverse outcomes but BP was much higher than in the INVEST.

Our study is one of few examining the relationship between RHR reduction and outcomes in treated patients. Although both treatment strategies reduced RHR, mean RHR at 24 months was significantly lower in the At strategy than in the Ve strategy. Despite previous studies showing a relationship between the degree of β-blocker heart rate lowering and outcome, there was no difference in outcome between the two treatment strategies either in the entire cohort or in the higher risk post-MI, diabetes, or gender subgroups. This observation suggests that verapamil may have additional beneficial effects beyond reduction of RHR by calcium antagonist activity at the sinus node. One possible explanation may relate to a sympatholytic effect,[33] as verapamil lowers catecholamine levels whereas β-blockers increase such levels. Additionally, all calcium antagonists are potent coronary arteriolar dilators.

Analyses of high-risk subgroups with diabetes or previous MI yielded similar results in terms of outcome and relationship with mean follow-up RHR. As previously reported,[25] the equivalence in clinical outcomes between the Ve and At strategies overall is especially remarkable considering the post-MI subgroup where β-blockers are standard for care for secondary prevention. Our data are consistent with the DAVIT II,[34] APSIS,[35] and other studies,[36] where beneficial effects of verapamil-SR were established in CAD patients with and without a history of prior MI and/or hypertension. In our prior MI subjects, the adverse outcome nadir was observed at a higher follow-up RHR than for the entire cohort (64 vs. 59 b.p.m.). The higher follow-up RHR nadir was consistent with the higher risk for adverse outcomes observed in these prior MI subjects. This may reflect autonomic compensation for limited cardiac performance as a result of prior MI that may begin before overt HF. Our report provides new information on RHR response by gender. For the same BP control, men and women had higher follow-up mean RHR with the Ve than with the At strategy, although no difference in clinical outcome was detectable. Consistent with previous studies,[14,16,31] women had a higher RHR than men, independent of treatment or comorbidities. Prior studies have suggested that the relationship between RHR and all-cause mortality is weaker in women than in men and that a higher RHR is a weak predictor of cardiovascular death in women.[17] Therefore, the high RHR in women may simply represent the extreme of normal distribution. Our results suggest that the predictive value is the same, but from a different (higher) reference RHR. In this elderly patient population with hypertension and CAD, for the same RHR, males have a greater risk of adverse outcomes.

When interpreting this analysis, one must consider its limitations. There is potential for selection bias when using controlled clinical trial instead of epidemiological cohorts. However, INVEST enrolled over 22 000 patients with hypertension and CAD and applied very few exclusion criteria (acute events and contraindications to study medications) that biased baseline demographics.[25] The INVEST population can be considered as all inclusive for stable CAD patients 50 and older who are candidates for either β-blocker or heart-rate-slowing calcium antagonist treatment. Also, there were relatively few patients and events at the lowest RHR levels, particularly in the subgroup analyses, and the results are specific to the study drugs and not to their respective drug classes. The role of β-blockers, in general, and particularly, atenolol in treatment of primary hypertension has recently been called into question.[37,38] However, in the INVEST, both the Ve and the At treatment strategies were similarly effective in BP control in a CAD population (at 24 months, 71.7% of Ve strategy patients and 70.7% of At strategy patients had BP below 140/90 mmHg).[25] This was likely related to use of twice daily atenolol dosing when the dose exceeded 50 mg/day as in most of the INVEST patients,[25] but was not the case for many prior hypertension trials.

Conclusion

Among elderly CAD patients with hypertension, high baseline RHR, as well as high and very low follow-up RHR, were associated with increased risk of adverse outcomes regardless of treatment strategy and underlying comorbidity such as diabetes or prior MI. Women had a higher RHR than men, whereas for the same RHR, men have greater risk of adverse outcomes. In addition to similar adverse outcome rates and BP control, a Ve strategy reduced RHR, although to a lesser extent than an At strategy, and may be an alternative therapy especially if β-blocker therapy is not appropriate for a particular patient.

Conflict of interest: none declared.

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