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

Rainer Kolloch¹, Udo F. Legler², Annette Champion³, Rhonda M. Cooper-DeHoff⁴, Eileen Handberg⁴, Qian Zhou³, and Carl J. Pepine⁴*

¹Medizinische Klinik, Evangelisches Krankenhaus Bielefeld, Akademisches Lehrkrankenhaus der Universität Münster, Bielefeld, Germany; ²Abbott GmbH & Co. KG, Ludwigshafen, Germany; ³Abbott, Abbott Park, Chicago, IL, USA; ⁴Division of Cardiovascular Medicine, University of Florida College of Medicine, 1600 SW Archer Road, PO Box 100277, Gainesville, FL 32610-0277, USA

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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
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.³–⁶ Among factors influencing RHR, the sympathetic nervous system (SNS) regulates both RHR and BP minute-by-minute as well as long term.⁷ An increase in RHR reflects decreased parasympathetic tone and/or increased sympathetic tone. RHR correlates with coronary artery disease (CAD)⁸–¹⁰ and a gender-related difference in this association, as well as with BP, has been suggested.¹¹,¹²

In CAD patients, therapies that decrease RHR appear more beneficial than those that increase RHR.¹³ RHR reduction, studied mostly from β-blocker trials of acute myocardial infarction (MI) or heart failure (HF), is associated with improved outcomes.¹⁴ Favourable effects have also been suggested for non-dihydropyridine calcium antagonists via effects on the SNS and RHR.¹⁵ Yet cardiac-slowing properties of antihypertensive drugs and associated effects on outcomes have not been studied in...
randomized trials in stable CAD or hypertension. 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. 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. 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 and secondary prevention according to the National Cholesterol Education Program 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 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. 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 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. 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 9.6% versus At 9.8% rate 36 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...
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.
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

<table>
<thead>
<tr>
<th>Baseline covariate</th>
<th>n/N</th>
<th>Event rate</th>
<th>HR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure (class I-II)</td>
<td>274/1182</td>
<td>23.18%</td>
<td>1.91 (1.67–2.18)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>882/6294</td>
<td>14.01%</td>
<td>1.78 (1.63–1.95)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Age (10 year increments)</td>
<td></td>
<td></td>
<td>1.64 (1.56–1.72)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>US residency</td>
<td>1908/16807</td>
<td>11.35%</td>
<td>1.64 (1.43–1.87)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>108/405</td>
<td>26.67%</td>
<td>1.57 (1.29–1.92)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Smoker</td>
<td>1198/10282</td>
<td>11.65%</td>
<td>1.41 (1.29–1.55)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>299/1570</td>
<td>19.04%</td>
<td>1.41 (1.24–1.60)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>959/7054</td>
<td>13.60%</td>
<td>1.34 (1.22–1.46)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>412/2517</td>
<td>15.74%</td>
<td>1.25 (1.12–1.40)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Coronary revascularization</td>
<td>827/5989</td>
<td>13.81%</td>
<td>1.17 (1.06–1.29)</td>
<td>0.001</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>220/1472</td>
<td>14.95%</td>
<td>1.16 (1.01–1.34)</td>
<td>0.04</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>1153/10600</td>
<td>10.88%</td>
<td>1.10 (1.01–1.21)</td>
<td>0.03</td>
</tr>
<tr>
<td>Heart rate (5 b.p.m. increments)</td>
<td></td>
<td></td>
<td>1.06 (1.04–1.08)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

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.
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 men vs. 4357 women, 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) 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), acute coronary syndromes, and HF. 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 and patients with CAD and hypertension in the Coronary Artery Disease Study.
Surgery Study (CASS) registry. These earlier studies suggested that RHR >75 and >77 b.p.m., respectively, were associated with increased risk of all-cause death and >83 b.p.m. for cardiovascular death. 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). 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

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

<table>
<thead>
<tr>
<th>Prior MI</th>
<th>Verapamil-SR strategy</th>
<th>Atenolol strategy</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>3546</td>
<td>3508</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Adverse outcome</td>
<td>467 (13.2%)</td>
<td>492 (14.0%)</td>
<td>0.93 (0.82–1.05)</td>
<td>0.24</td>
</tr>
<tr>
<td>Death</td>
<td>372 (10.5%)</td>
<td>366 (10.4%)</td>
<td>1.00 (0.86–1.15)</td>
<td>0.99</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>67 (1.9%)</td>
<td>79 (2.3%)</td>
<td>0.83 (0.60–1.15)</td>
<td>0.27</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>50 (1.4%)</td>
<td>67 (1.9%)</td>
<td>0.73 (0.51–1.06)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No prior MI</th>
<th>Verapamil-SR strategy</th>
<th>Atenolol strategy</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>7548</td>
<td>7590</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Adverse outcome</td>
<td>606 (8.0%)</td>
<td>604 (8.0%)</td>
<td>1.02 (0.91–1.14)</td>
<td>0.80</td>
</tr>
<tr>
<td>Death</td>
<td>463 (6.1%)</td>
<td>477 (6.3%)</td>
<td>0.98 (0.86–1.12)</td>
<td>0.78</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>77 (1.0%)</td>
<td>74 (1.0%)</td>
<td>1.05 (0.76–1.45)</td>
<td>0.75</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>78 (1.0%)</td>
<td>75 (1.0%)</td>
<td>1.05 (0.77–1.44)</td>
<td>0.76</td>
</tr>
</tbody>
</table>

MI, myocardial infarction; NA, not applicable.
between risk of adverse outcomes and baseline RHR observed here is consistent with recent findings from other patients with CAD. 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, supporting that on treatment RHR contributes more information to the prediction of adverse outcomes. This has relevance to the report from the Syst-Eur trial, 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, 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, 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, APSIS, and other studies, 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 was observed at a higher follow-up RHR than for the Ve strategy patients had BP below 140/90 mmHg. This was likely related to a greater risk of adverse outcomes as well as lower follow-up 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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References