Is there benefit of cardiac slowing drugs in the treatment of hypertensive patients with elevated heart rate?

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This editorial refers to ‘Impact of resting heart rate on outcomes in hypertensive patients with coronary artery disease: findings from the INternational VErapamil-SR/trandolapril STudy (INVEST)’ by R. Kolloch et al., on page 1327

A large body of evidence indicates that resting heart rate is a strong independent predictor of cardiovascular morbidity and mortality.1–9 This association has been found to be present at all ages and in different clinical settings, irrespective of the presence of co-morbidities.1–9 The relationship was still present when subjects who died within the first years after baseline evaluation were excluded, thereby ruling out the possibility that the association between heart rate and mortality was due to some underlying chronic disease unrecognized at the time of baseline assessment.1,4,7 Overall, the results of ~50 longitudinal studies have been published on the relationship between heart rate and total and/or cardiovascular mortality, and the large majority have demonstrated that heart rate is a strong predictor of risk whereas no study has shown the reverse.8–11 The pathogenetic mechanisms accounting for the connection between high heart rate, atherosclerosis, and cardiovascular morbidity have been documented in many laboratory and clinical studies, reinforcing the clinical validity of the epidemiologic data.12,13 A crucial step is obviously to know whether heart rate is still associated with mortality when controlling for a variety of cardiovascular risk factors. All but one analysis demonstrated that heart rate was an independent risk factor and that the risk was graded across the heart rate range.8,9 On the basis of this evidence, heart rate has been included by several Scientific Authorities into scoring systems that can be used to predict all-cause mortality risk.14,15 In the clinical score sheet developed by the Cooper Clinic panelists, high heart rate received as many risk factor points as hypertension or low cardiorespiratory fitness assessed with exercise testing.14 The main goal of a clinical score sheet is to help healthcare practitioners to identify and provide strategies for high-risk subjects who may benefit from therapeutic interventions. For heart rate, a benefit from cardiac slowing treatment has been demonstrated in subjects with myocardial infarction or congestive heart failure.10,11 A recent meta-regression of randomized clinical trials in post-myocardial infarction patients strongly suggests that the beneficial effect of β-blockers and calcium channel blockers in this clinical setting is proportionally related to resting heart rate reduction.10 An interesting aspect of this study was the absence of residual heterogeneity that could be interpreted as all the benefit is brought by resting heart rate reduction without any other mechanism accounting for the reduction in mortality. According to this meta-analysis, each 10 bpm reduction in resting heart rate was estimated to reduce the relative risk of cardiac death by ~30%, the risk of sudden death by 39%, and the risk of all-cause mortality by 20%.10 Similar results were found in patients with systolic chronic heart failure. β-Blockers improve cardiac function and prolong survival in congestive heart failure, but it is still unclear whether a close relationship exists between heart rate reduction and clinical outcomes with these agents. In a recent meta-analysis by Flannery et al. encompassing 35 trials, which included 22,926 patients, the authors analysed the association between change in heart rate, all-cause mortality, and left ventricular ejection fraction.11 A close relationship between all-cause annualized mortality rate and heart rate was found. In addition, a strong correlation was observed between reduction of heart rate and improvement of ejection fraction. The results of this meta-analysis indicate that a major contributor to the clinical benefits of β-blocker therapy in congestive heart failure is the heart rate-lowering effect of these agents and that the magnitude of heart rate reduction is more important than the achievement of target dose of β-blockers.

To date, no clinical trial has been performed to demonstrate the efficacy and the risk–benefit ratio of cardiac slowing treatment in patients without cardiac disorders, making it difficult to make...
specific treatment recommendations for non-cardiac patients. In particular, the relationship between pharmacological heart rate reduction and outcome has never been assessed in patients with hypertension. Thus, the analysis of the INternational VErapamil SR/Trandolapril STudy (INVEST) by Kolloch et al.\textsuperscript{16} provides new important information. INVEST participants are patients aged 50 years or older with essential hypertension requiring drug therapy and with documented stable coronary artery disease (CAD). In agreement with previous results obtained in hypertensive individuals and CAD patients, in the INVEST study a linear relationship was found between baseline heart rate and adverse outcome. The novelty of this investigation is that mean follow-up heart rate calculated from all follow-up visits was also tested as a predictor of outcome in the Cox regression analysis. The INVEST participants were randomly assigned to either verapamil sustained release or atenolol treatment.\textsuperscript{16} Trandolapril and/or hydrochlorothiazide was administered to achieve blood pressure goals. After 2 years of treatment, heart rate was reduced by \(\approx 6.5\) bpm in the atenolol arm and by \(\approx 3\) bpm in the verapamil arm. Mean follow-up heart rate was strongly associated with risk of all-cause death, non-fatal myocardial infarction, or non-fatal stroke, and a J-shaped relationship was observed. An important finding was that follow-up heart rate excluded baseline heart rate from the Cox model when both heart rates were tested in the same regression analysis, indicating that on-treatment heart rate is a more important predictor of outcome than pre-treatment heart rate when cardiac slowing drugs are used.

Whether the relationship between heart rate and adverse outcome is linear or non-linear is not well known. For a putative risk factor it is important to establish if the association with outcome is described by a J-shaped or a U-shaped relationship because this has implications for the identification of the optimal target level. In all but a few studies, no increased risk of mortality was found for the lower extreme of the heart rate distribution, but those analyses were performed mostly in untreated individuals.\textsuperscript{8,9} The J-shaped relationship between follow-up heart rate and outcome found in the INVEST study suggests that an upturn in mortality or non-fatal events may occur if heart rate is reduced by treatment to \(< 59\) bpm.\textsuperscript{16} However, it is interesting to observe that this cut-off level may vary according to co-morbidities. In patients with diabetes, the risk nadir was at 61 bpm and in patients with history of myocardial infarction the nadir was at 63 bpm. These data suggest that caution should be used toward excessive heart rate reduction in hypertensive patients with CAD especially when important co-morbidities are present. However, on the basis of the INVEST results, it is difficult to identify specific threshold values beyond which heart rate reduction should be considered hazardous. In fact the risk nadirs varied greatly according to whether patients were treated with verapamil or atenolol (62 vs 51 bpm, respectively) and according to gender (57 bpm for men and 64 bpm for women). In most previous studies, the predictive value of elevated heart rate for mortality has been found to be weaker in women than in men, and in some studies no association between heart rate and cardiovascular mortality was observed among women.\textsuperscript{8,9} In particular, high heart rate appeared to be a weak predictor of death from CAD in the female gender. However, according to the INVEST results, the heart rate–risk relationship was present in both genders, as no significant interaction of gender with either baseline or follow-up heart rate was observed.\textsuperscript{16}

The upper normal limits of resting heart rate have not been established.\textsuperscript{8,9} The reference range in adults is nominally between 60 and 100 bpm. This normality interval clearly does not apply to heart rate considered as a cardiovascular risk factor, as shown by the results of the INVEST study.\textsuperscript{16} In agreement with many epidemiological studies, a considerable increase in the risk was observed for pre-treatment heart rate levels \(> 80–85\) bpm. As expected, the threshold value was lower for on-treatment heart rate, and the association with increased risk was apparent with a mean follow-up heart rate \(> 75\) bpm. Does this mean that in hypertensive patients we should pursue a target heart rate lower than 75 bpm? The data provided by the INVEST analysis cannot give an answer to this question.\textsuperscript{16} The median verapamil dose (240 mg) was the same within the three groups of baseline and follow-up heart rates, and the median atenolol dose was even greater in the groups with heart rate \(> 60\) bpm (100 mg/day). Whether increasing these doses in patients with a heart rate \(> 75\) bpm would prevent more events cannot be established because the study was not designed to clarify this point.

Conclusions

Resting heart rate is a strong predictor of mortality in hypertensive subjects and CAD patients.\textsuperscript{3,4} The INVEST results confirm the association of heart rate with mortality in this clinical setting.\textsuperscript{16} However, in clinical practice, heart rate is not yet considered as a classical cardiovascular risk factor. This gap between epidemiological data and clinical practice is mainly explained by the fact that the clinical benefit of heart rate reduction has not been proved in the non-cardiac patient. The results of the INVEST study offer important new information on this issue because they show that a fast heart rate after administration of antihypertensive drugs provided with cardiac slowing properties is strongly associated with mortality and non-fatal cardiovascular events. A limitation of the study is that the INVEST population consisted of hypertensive subjects with CAD. Therefore, the extent to which the INVEST findings can be generalized to a population of non-CAD subjects is unclear. This consideration applies especially to the upturn in mortality found for the lower extreme of the heart rate distribution. Whether drug-induced heart rate reduction can actually delay cardiovascular events in hypertension will be clarified by large-scale, double-blinded, placebo-controlled clinical studies.

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References


