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Effect of Beta-Blocker Therapy, Maximal Heart Rate and Exercise Capacity during Stress Testing on Long-Term Survival (From the FIT Project)

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Abstract

Whether lower heart rate thresholds (as defined by percentage of predicted maximal heart rate, ppMHR) should be utilized to determine chronotropic incompetence in patients on beta-blocker therapy (BBT) remains unclear. In this retrospective cohort study, we analyzed 64,549 adults without congestive heart failure or atrial fibrillation (54±13 years old, 46% women, 29% black) who underwent clinician-referred exercise stress testing at a single healthcare system in Detroit, Michigan between 1991–2009, with median follow-up of 10.6 years for all-cause mortality (IQR 7.7–14.7 years). Using Cox regression models, we assessed the effect of BBT, ppMHR and estimated exercise capacity on mortality, with adjustment for demographic data, medical history, pertinent medications, and propensity to be on BBT. There were 9,259 deaths during follow-up. BBT was associated with an 8% lower adjusted achieved ppMHR (91% in no-BBT vs. 83% in BBT). ppMHR was inversely associated with all-cause mortality, but with significant attenuation by BBT (per-10%-ppMHR HR: no-BBT: 0.80 (0.78–0.82) vs. BBT: 0.89 (0.87–0.92)). Patients on BBT who achieved 65% ppMHR had a similar adjusted mortality rate as those not on BBT who achieved 85% ppMHR ($P>.05$). Estimated exercise capacity further attenuated the prognostic value of ppMHR (per-10%-ppMHR HR: no-BBT: 0.88 (0.86–0.90) vs. BBT: 0.95 (0.93–0.98)). In conclusion, the prognostic value of ppMHR was significantly attenuated by BBT. For patients on BBT, a lower threshold of 65% ppMHR may be considered for determining worsened prognosis.

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Disclosures

The authors have no relevant conflicts of interest to report, including financial interests, activities, relationships, and affiliations.

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Estimated exercise capacity further diminished the prognostic value of ppMHR particularly in patients on BBT.

Keywords

Beta Blocker Therapy; Maximal Heart Rate; Exercise Capacity; Mortality

Introduction

Chronotropic incompetence—the inability to appropriately increase heart rate to accommodate increased physiologic demands—is a powerful and independent predictor of mortality in both healthy individuals,^{1–8} and in those with chronic medical conditions.^{9–14} Nevertheless, despite its prognostic utility, chronotropic incompetence remains underappreciated in clinical practice,^{1,9} in part from the potential confounding effects of beta blocker therapy (BBT), and the multitude of heart rate thresholds and equations derived for this patient population.^{1,7,11–13,15} Notably, exercise capacity is also a powerful predictor of survival,^{16–20} however, the combined effect of exercise capacity and BBT on the prognostic value of peak exertional heart rate remains unexplored. Whether lower heart rate thresholds should be used in patients on BBT represents an important area of uncertainty. Therefore, in this study, we aimed to describe the interaction between peak exertional heart rate (defined as the percentage of age-predicted maximal heart rate achieved, or ppMHR), BBT, and estimated exercise capacity on the risk for all-cause mortality in a large cohort of men and women without heart failure who were clinically referred for exercise stress testing. We hypothesized that lower ppMHR would be associated with greater mortality risk, and that this association would be attenuated by both BBT and higher exercise capacity.

Methods

This study is based on data from the Henry Ford Exercise Testing Project (The FIT Project), a retrospective cohort study aimed at investigating the long-term implications of estimated exercise capacity on all-cause mortality.²¹ The FIT Project is unique in its combined use of: 1) directly measured exercise data; 2) retrospective collection of medical history and medication treatment data taken at the time of the stress test; and 3) retrospective supplementation of supporting clinical data using the electronic medical record (EMR) and administrative databases.

The FIT Project cohort represents a registry of 69,885 consecutive patients who underwent clinician-referred treadmill stress testing at Henry Ford Health System in metropolitan Detroit, MI between 1991 and 2009.²¹ These medical centers are part of a large, vertically-integrated organization that provides healthcare and offers a managed care insurance plan. Treadmill, medical history, and medication data were collected by exercise physiologists and nurses, and entered at the time of testing into a common clinical reporting tool that directly populated the EMR. Supporting clinical data were derived from the EMR and administrative databases shared across Henry Ford Health System. Data from The FIT Project was gathered retrospectively, de-identified in the dataset, and approved by the Henry Ford Health System Institutional Review Board.

We considered patients from The FIT Project cohort excluding those with a baseline history of heart failure (n=1,579) and atrial fibrillation (n=1,975). Patients were further excluded if any covariates of interest were missing (n=1,967), leaving a study cohort of 64,549 individuals. Patients were categorized according to baseline BBT, with 13,608 (21%) patients on BBT and 50,941 (79%) patients not on BBT at the time of stress testing.

All patients underwent routine, clinically-referred, symptom-limited treadmill stress testing following the standard Bruce protocol.²² For individuals with repeat stress testing, only the results from the first test were considered in the registry. Patients less than 18 years old at the time of stress testing and patients tested using non-Bruce protocol tests were not included in the registry. In accordance with clinical guidelines,²³ symptom limited treadmill testing was terminated at the discretion of the supervising clinician for reasons that included significant arrhythmias, abnormal hemodynamic responses, diagnostic ST-segment changes, exercise-limiting symptoms such as chest pain or shortness of breath, or if the patient was unwilling or unable to continue. Resting heart rate and blood pressures were taken prior to stress testing by clinical personnel. Peak exertional heart rate during exercise testing was recorded. The maximal age-predicted heart rate used to calculate ppMHR was defined as 220-age in the main analyses, with alternative calculations provided by *Brawner, et al*,¹⁵ and *Tanaka, et al*,²⁴ available in sensitivity analyses. Chronotropic incompetence was defined by a threshold of 85% ppMHR.¹ Estimated exercise capacity, expressed as estimated metabolic equivalents of task (estMETs), was calculated by the treadmill controller system (Q-Stress, Quinton Instruments, Bothell, WA) using peak speed and grade based on equations reported by the American College of Sports Medicine.²⁵

A medical history including age, sex, race, indication for testing, risk factor burden, active medication use, and past medical history was obtained by trained nurses and/or exercise physiologists immediately prior to the stress test. Race was defined exclusively by self-report. Obesity was defined by clinician report at the time of stress testing or body mass index (BMI) ≥ 30 kg/m². Smoking history was defined as self-reported smoking at the time of testing. Family history of CAD was defined as a self-reported history of CAD in a first degree relative. Indication for stress testing was extracted from the stress test requisition provided by the referring clinician, and subsequently categorized into common indications (chest pain, shortness of breath, pre-operative evaluation, etc.). Information on medication use and past medical history were supplemented by a retrospective search of the EMR, administrative databases, and/or pharmacy claims files from enrollees in the integrated health plan. A database-verified diagnosis was considered present when the appropriate International Statistical Classification of Diseases and Related Health Problems 9th (ICD-9) code was present on ≥ 3 separate encounters within the health system. Diabetes mellitus, hyperlipidemia, and hypertension were defined as a self-reported prior diagnosis, a database-verified diagnosis, and/or use of medications for each medical condition. Known CAD was defined as prior myocardial infarction (MI), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), or documented CAD on a prior angiogram.

Mortality was ascertained in April 2013, after federal law changes in 2011 limited reporting of certain deaths by state agencies.²⁶ An algorithmic search of the Social Security Death

Index (SSDI) Death Master File (DMF) was completed using social security number, first name, last name, and date of birth data.

Baseline groups, stratified by use of BBT, were compared using chi-squared testing or analysis of variances techniques as appropriate. We used Cox proportional hazards regression models to calculate hazard ratios (HR) associated with decreasing strata of ppMHR. We considered the propensity for patients to be on BBT, and a propensity score was derived from logistic regression models adjusting for age, sex, race, history of CAD, MI, PCI, CABG, diabetes, obesity or smoking, use of angiotensin receptor blockers, ACE inhibitors, calcium channel blockers and aspirin, and date of stress testing to account for secular trends in the prescription of beta-blockers. The propensity score models enable assessment of the survival benefits from the chronotropic effects and other pleiotropic mechanisms associated with BBT.

We also sought to obtain adjusted mortality rates at the median follow-up time of 10.6 years (IQR 7.7 – 14.7 years) as a function of ppMHR using a margins of response logistic regression model,²⁷ which similarly accounts for differences in comorbidity burden and other baseline characteristics between those on and not on BBT. The advantage of this statistical model is that it provides absolute adjusted mortality rates (instead of only relative risk) that are potentially more intuitive and readily comparable (i.e. BBT vs. no BBT) at specific ppMHR thresholds than results from traditional Cox regression models. Both Cox regression and margins of response models were adjusted for age, sex, race, resting systolic and diastolic blood pressure, history of diabetes, hyperlipidemia, hypertension, obesity, smoking, CAD, PCI, CABG, MI, family history of CAD, use of medications for COPD and hypertension, use of angiotensin receptor blockers, ACE inhibitors, calcium channel blockers, aspirin and statins, and indication for stress testing. Additional adjustment for estMETs as a continuous variable was performed in augmented models as a mediation analysis.

In graphical analyses examining the association between ppMHR and adjusted mortality rate, a fractional polynomial trend line was generated and superimposed on the data to clearly display the relationship between the two variables of interest. Statistical analyses were performed using Stata (version 13.1, 2014; StataCorp, College Station, Texas).

Results

Table 1 shows the baseline characteristics for the study cohort. Patients on BBT were older, more likely to have medical comorbidities, and use cardiovascular medications including aspirin and statins ($P < .001$ for all covariates). Table 2 shows the stress test results for the study cohort. Those on BBT had lower resting and peak exertional heart rates, lower estimated exercise capacity, and were less likely to achieve 85% ppMHR ($P < .001$ for all covariates). In adjusted multivariate models, BBT was associated with a consistent 8% lower ppMHR compared to those not on BBT, even when stratified by sex and baseline CAD status (Table 3).

There were 9,259 deaths observed over a median follow-up period of 10.6 years (IQR 7.7–14.7 years). The unadjusted mortality rate at the median follow-up time was 8.1% and 14.4% in patients not on, and on BBT, respectively.

Table 4 shows the prognostic value of ppMHR, with ppMHR analyzed as a continuous variable, without and with further adjustment for estimated exercise capacity. For patients not on BBT, each 10% lower ppMHR was associated with a 20% increased mortality risk that was attenuated by exercise capacity. Notably, BBT significantly blunted the inverse association between ppMHR and mortality ($P<.001$). For patients on BBT, each 10% lower ppMHR was associated with only a 12% increased mortality risk. Importantly, the prognostic value of ppMHR was greatly attenuated by exercise capacity, and was completely abrogated in certain subpopulations, such as in men on BBT and in those with CAD on BBT ($P>.050$) (eTable 1).

Table 5 shows the propensity score-matched hazard ratios associated with decreasing strata of ppMHR, stratified by use of BBT without (A) and with (B) further adjustment for estimated exercise capacity. An inverse association between ppMHR and mortality was again observed, with attenuation by both BBT and estimated exercise capacity ($P<.001$ for all). When exercise capacity was not taken into account, patients not on BBT who achieved 75–84% ppMHR had a 77% increased risk for mortality compared to those who achieved 85% ppMHR (the referent group). Notably, in patients on BBT, this degree of increased mortality risk was only observed in those who achieved <65% ppMHR.

Figure 1 shows the adjusted absolute mortality rate by ppMHR evaluated at the median follow-up period, without (A) and with (B) further adjustment for estimated exercise capacity. In patients not on BBT, the inverse association between ppMHR and adjusted mortality rate was mostly linear between the ranges of 65% to 90% ppMHR, before plateauing with greater ppMHR achieved. In marked contrast, in patients on BBT, the relationship between ppMHR and the adjusted mortality rate was significantly attenuated particularly when ppMHR was greater than 65% ($P<.001$). Notably, patients on BBT who achieved approximately 65% ppMHR had a similar adjusted mortality rate of 11% as patients not on BBT achieving 85% ppMHR who had a similar comorbidity burden ($P>.050$).

Sensitivity analyses were independently performed excluding those who i) died within 1 year of their stress test ($n=407$), ii) had diabetes mellitus or known CAD ($n=18,574$), or iii) underwent stress testing for pre-operative cardiac evaluations ($n=1,309$). We further adjusted for iv) the decade in which each stress test took place to account for cohort effects including improvements in management of chronic diseases over time ($n=64,549$), and v) body mass index (BMI) ($n=40,414$) in patients for whom data was collected. Overall, there were no clinically significant changes to our main results (eTable 2). Similar results were obtained when the prognostic value of exertional heart rate was examined using the proportion of heart rate reserve used during peak exercise $[(HR_{peak} - HR_{rest}) / (Age-Predicted MHR - HR_{rest})]$ (eTable 3). Given the current debates on the optimal estimation of maximal heart rate, we further repeated our analyses based on heart rate equations reported by *Tanaka, et*

al. and *Brawner, et al.* in their respective cohorts,^{15,24} without clinically significant differences being observed in the prognostic value of ppMHR (eTable 4).

Discussion

Our study has important consequences for using exercise data from routine stress tests to risk stratify patients on BBT. BBT was associated with a consistent 8% lower ppMHR in our cohort. Despite ppMHR being inversely associated with mortality risk, this association was notably blunted in patients on BBT. Consistent with our primary research hypothesis, the association between ppMHR and mortality was further attenuated with additional consideration for exercise capacity, particular in those on BBT. Our results suggest that prognosis associated with low ppMHR must be interpreted in the context of BBT and exercise capacity achieved.

Low ppMHR is reported to be a powerful and independent predictor of mortality,^{7,8,28} and was shown to only be minimally affected by beta-blockade in a large cohort of veteran men on BBT.⁸ In the present study, we showed that ppMHR remains an independent predictor of survival regardless of BBT. However, in marked contrast to prior studies, BBT significantly attenuated the higher mortality risk associated with lower ppMHR, suggesting that using different heart rate thresholds may be justified among patients on BBT. Our discrepancies in findings may be due to differences between veteran and non-veteran populations—namely our inclusion of women in our cohort, different body compositions, disease burdens, medical therapies, medication adherences, and accessibility to healthcare—and differences in length of follow-up and consideration of confounders.

Given the prognostic value of exercise capacity that is well-recognized within the literature,^{16–20} we assessed whether exercise capacity modulates the relationship between ppMHR and BBT on mortality. Previously, it was reported that exercise capacity did not abrogate the prognostic value of ppMHR, notably in a cohort of patients not on BBT.²⁸ However, in our cohort, additional consideration for exercise capacity greatly attenuated the prognostic value of ppMHR in all patients, but especially in those on BBT, suggesting that exercise capacity likely mediates some of the association between ppMHR and survival. In contrast to prior studies, while both ppMHR and exercise capacity remained independent predictors of survival, we found that ppMHR became almost clinically irrelevant and added little additional prognostic value in patients on BBT once exercise capacity was considered.

One question often asked in clinical practice is how to interpret low ppMHR in patients on BBT. First and foremost, our study suggests that these patients do not have as worse a prognosis as one might expect due to the prognostic value of ppMHR being blunted by BBT. For patients who have low ppMHR during exercise stress testing, careful interpretation of the results with full consideration for use of BBT and exercise capacity achieved is needed, as failure to consider the full clinical picture may result in inaccurate prognosis, and unnecessary diagnostic studies and further workup.

Since ppMHR is still widely used in clinical practice and exercise capacity has yet to be routinely incorporated into risk stratification tools, it may be reasonable to use a lower heart rate threshold such as 65% ppMHR in patients on BBT to help determine worsened prognosis (vs. 85% ppMHR in patients not on BBT). At this lower heart rate threshold, patients on BBT had an equivalent prognosis compared to those not on BBT who achieved 85% ppMHR and had a similar comorbidity burden. However, greater attention should ultimately be placed on exercise capacity for prognosis and risk stratification, given that low ppMHR carries little additional prognostic information once BBT and exercise capacity are taken into account.

Our study has multiple limitations. We examined a referral population that is likely enriched in comorbidities compared to healthier cohorts. We lacked information on the dosage and type of beta-blocker prescribed (β 1-selective versus others), and whether medications were withheld the day before exercise stress testing. Sensitivity analyses were performed to minimize potential biases and did not result in significant changes to our findings. Important determinants of survival and use of BBT such as frailty, substance use, diet, physical activity, depression, other comorbidities and accessibility to healthcare may not have been fully accounted for, but were minimized through use of propensity score matching statistical models. Cohort effects from changes in secular trends involving smoking, diet, and medical management may have been present but did not significantly alter our findings in sensitivity analyses. Medical history was derived partly through self-report and presumed indications for medications, which may have been prescribed for other conditions. Sensitivity analyses were conducted to control for confounders from misclassifications in medical history with no significant changes to our results.

Despite gender and racial diversity in our cohort, geographic and survivorship biases may be present from our study criteria. We lacked data to identify patients whose tests were prematurely terminated due to symptoms or diagnostic findings. While our determination of exercise capacity may have been an overestimation in some patients, the derivation of estMETs that we reported is widely used in clinics today. Our results were derived from an initial stress test that may not reflect the patients' true ppMHR and exercise capacity due to symptomatic complaints; however, this approach is representative of what is seen clinically and therefore is of clinical relevance.

Last but not least, some may reason that a direct comparison of mortality between BBT groups may not be meaningful as patients on BBT have a greater comorbidity burden, a problem inherent with all retrospective studies. However, testing our hypothesis on a large scale through a prospective design or a randomized controlled trial would be impractical and prohibitively expensive. Therefore, we opted for a retrospective design in which we sought to minimize these concerns by accounting for differences between BBT groups through use of propensity score matching and other statistical methods that allow for meaningful comparison.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Adjusted mortality rate by percentage of age-predicted maximal heart rate. Results stratified by beta-blocker groups without (A) and with (B) further adjustment for estimated exercise capacity. 95% confidence intervals and estimated polynomial trend lines shown. Significant interactions ($p < 0.01$) between percentage of age-predicted maximal heart rate, beta-blocker therapy, and exercise capacity existed without significant change in the results. Results adjusted for age, sex, race, resting systolic and diastolic blood pressure, history of diabetes, hyperlipidemia, hypertension, obesity, smoking, coronary artery disease, percutaneous

coronary intervention, coronary artery bypass graft, myocardial infarction, family history of coronary artery disease, use of medications for chronic obstructive pulmonary disease and hypertension, use of angiotensin receptor blockers, angiotensin-converting-enzyme inhibitors, calcium channel blockers, aspirin, and statins, and indication for stress testing.

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Table 1

Baseline Characteristics

Variable	Total Cohort (n=64,549)	Beta Blocker Therapy		p-value
		No (n=50,941)	Yes (n=13,608)	
Age (years)	54 ± 13	53 ± 13	59 ± 12	<.001
Women	29,856 (46%)	23,788 (47%)	6,068 (45%)	<.001
White	41,430 (64%)	32,855 (65%)	8,575 (63%)	<.001
Black	18,704 (29%)	14,417 (28%)	4,287 (32%)	<.001
Obesity	41,812 (65%)	32,704 (64%)	9,108 (67%)	<.001
Smoker	27,034 (42%)	21,139 (41%)	5,895 (43%)	<.001
Hypertension	35,950 (56%)	28,012 (55%)	7,938 (58%)	<.001
Diabetes mellitus	12,345 (19%)	8,870 (17%)	3,475 (26%)	<.001
Hyperlipidemia	29,002 (45%)	21,241 (42%)	7,761 (57%)	<.001
Coronary artery disease	8,571 (13%)	4,066 (8%)	4,505 (33%)	<.001
Myocardial infarction	6,823 (11%)	3,229 (6%)	3,594 (26%)	<.001
Percutaneous coronary intervention	2,647 (4%)	905 (2%)	1,742 (13%)	<.001
Coronary artery bypass graft	2,215 (3%)	1,028 (2%)	1,187 (9%)	<.001
Family history of coronary artery disease	32,774 (51%)	25,919 (51%)	6,855 (50%)	.295
Indication for Stress Test:				p-value
Chest pain	42,245 (65%)	32,906 (65%)	9,339 (68%)	<.001
Dyspnea	5,573 (9%)	4,568 (9%)	1,005 (7%)	<.001
Pre-operation evaluation	1,309 (2%)	999 (2%)	310 (2%)	.020
Medications				p-value
Hypertension medications	24,646 (38%)	16,708 (33%)	7,938 (58%)	<.001
Angiotensin-converting-enzyme inhibitor	11,714 (18%)	7,677 (15%)	4,037 (30%)	<.001
Angiotensin receptor blocker	1,770 (3%)	1,110 (2%)	660 (5%)	<.001
Calcium channel blocker	8,707 (13%)	6,193 (12%)	2,514 (18%)	<.001
Statin	13,475 (21%)	8,436 (17%)	5,039 (37%)	<.001
Aspirin	14,102 (22%)	8,426 (17%)	5,676 (42%)	<.001
Chronic obstructive pulmonary disease medications	5,617 (9%)	4,660 (9%)	957 (7%)	<.001

Baseline characteristics for the study cohort. P-value between beta-blocker groups.

Table 2**Stress Test Results**

Variable	Total Cohort (n=64,549)	Beta Blocker Therapy		p-value
		No (n=50,941)	Yes (n=13,608)	
Resting systolic blood pressure (mm Hg)	131 ± 19	130 ± 19	135 ± 20	<.001
Resting diastolic blood pressure (mm Hg)	81 ± 10	81 ± 10	82 ± 11	<.001
Resting heart rate (beats per minute)	73 ± 13	74 ± 12	68 ± 12	<.001
Peak exercise heart rate (beats per minute)	148 ± 22	153 ± 19	130 ± 23	<.001
Achieved 85% of age-predicted maximal heart rate	48,969 (76%)	43,137 (85%)	5,832 (43%)	<.001
Mean metabolic equivalents achieved	9.0 ± 3	9.2 ± 3	8.0 ± 3	<.001
<6 metabolic equivalents	10,029 (16%)	6,830 (13%)	3,199 (24%)	<.001
6–10 metabolic equivalents	17,883 (28%)	13,209 (26%)	4,674 (34%)	<.001
10–12 metabolic equivalents	22,777 (35%)	18,586 (36%)	4,191 (31%)	<.001
>12 metabolic equivalents	13,860 (21%)	12,316 (24%)	1,544 (11%)	<.001

Stress test results for the study cohort. Age-predicted maximal heart rate estimated by = 220 – age. P-value between beta-blocker groups.

Table 3

Adjusted Percentage of Age-Predicted Maximal Heart Rate Achieved

Percentage of Age-Predicted Maximal Heart Rate Achieved	Beta-Blocker Therapy		p-value
	No (n=50,941)	Yes (n=13,608)	
Total Cohort (n=64,549)	91% (91%–91%)	82% (82%–83%)	<.001
Men (n=34,693)	91% (91%–91%)	82% (82%–83%)	<.001
Women (n=29,856)	91% (91%–92%)	82% (82%–83%)	<.001
No Established Coronary Artery Disease (n=55,978)	92% (92%–92%)	83% (83%–84%)	<.001
Established Coronary Artery Disease (n=8,571)	86% (85%–86%)	77% (77%–78%)	<.001

Adjusted percentage of age-predicted maximal heart rate and exercise capacity achieved in the total cohort and select subpopulations by beta blocker groups. Age-predicted maximal heart rate determined as $220 - \text{age}$. P-value between beta-blocker groups. Similar results were obtained with alternative models predicting maximal heart rate.

Results adjusted for age, sex, race, resting systolic and diastolic blood pressure, history of diabetes, hyperlipidemia, hypertension, obesity, smoking, coronary artery disease, percutaneous coronary intervention, coronary artery bypass graft, myocardial infarction, family history of coronary artery disease, use of medications for chronic obstructive pulmonary disease and hypertension, use of angiotensin receptor blockers, angiotensin-converting-enzyme inhibitors, calcium channel blockers, aspirin, and statins, and indication for stress testing.

Table 4

Prognostic Value of the Percentage of Age-Predicted Maximal Heart Rate Achieved: Continuous Analysis

HR per 10% ppMHR	A. No Adjustment for Exercise Capacity	B. Adjustment for Exercise Capacity	p-value
All Patients (n=64,549)	0.84 (0.83–0.86)	0.91 (0.89–0.92)	<.001
No Beta Blocker Therapy (n=50,941)	0.80 (0.78–0.82)	0.88 (0.86–0.90)	<.001
Beta Blocker Therapy (n=13,608)	0.89 (0.87–0.92)	0.95 (0.93–0.98)	<.001

Prognostic value of percentage of age-predicted maximal heart rate, without (A) and with (B) additional adjustment for exercise capacity, stratified by use of beta-blocker therapy. Age-predicted maximal heart rate determined by $220 - \text{age}$, and hazard ratios results displayed as per 10% of age-predicted maximal heart rate, with 95% confidence intervals shown. P-value between beta-blocker groups. Models adjusted for age, sex, race, resting systolic and diastolic blood pressure, history of diabetes, hyperlipidemia, hypertension, obesity, smoking, coronary artery disease, percutaneous coronary intervention, coronary artery bypass graft, myocardial infarction, family history of coronary artery disease, use of medications for chronic obstructive pulmonary disease and hypertension, use of angiotensin receptor blockers, angiotensin-converting-enzyme inhibitors, calcium channel blockers, aspirin, and statins, and indication for stress testing.

Table 5

Prognostic Value of Percentage of Age-Predicted Maximal Heart Rate, Stratified by Heart Rate Achieved

A. Without Adjustment for Exercise Capacity			
ppMHR	Beta Blocker Therapy		p-value
	No	Yes	
85% (n=48,969)	1.00 (referent)	1.16 (1.07–1.25)	<.001
75–84% (n=8,616)	1.77 (1.66–1.89)	1.40 (1.29–1.52)	<.001
65–74% (n=4,675)	2.20 (2.02–2.40)	1.45 (1.33–1.58)	<.001
<65% (n=2,289)	2.38 (2.12–2.67)	1.84 (1.67–2.02)	<.001
B. With Adjustment for Exercise Capacity			
ppMHR	Beta Blocker Therapy		p-value
	No	Yes	
85% (n=48,969)	1.00 (referent)	1.15 (1.06–1.24)	.001
75–84% (n=8,616)	1.34 (1.26–1.43)	1.27 (1.17–1.38)	.281
65–74% (n=4,675)	1.38 (1.27–1.51)	1.17 (1.07–1.27)	.003
<65% (n=2,289)	1.23 (1.10–1.39)	1.18 (1.07–1.30)	.543

Prognostic value of percentage of age-predicted maximal heart rate stratified by use of beta-blocker therapy, without (A) and with (B) additional adjustment for exercise capacity. Age-predicted maximal heart rate determined by $220 - \text{age}$. P-value between beta-blocker therapy groups. Models adjusted for the propensity to be on beta-blockers, in addition to age, sex, race, resting systolic and diastolic blood pressure, history of diabetes, hyperlipidemia, hypertension, obesity, smoking, coronary artery disease, percutaneous coronary intervention, coronary artery bypass graft, myocardial infarction, family history of coronary artery disease, use of medications for chronic obstructive pulmonary disease and hypertension, use of angiotensin receptor blockers, angiotensin-converting-enzyme inhibitors, calcium channel blockers, aspirin and statins, and indication for stress testing.