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Validation of prognostic value of the hemodynamic gain index in different groups of patients undergoing exercise stress testing

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Abstract

Background: Recently, the hemodynamic gain index (HGI) has shown to be a strong independent predictor of all-cause mortality and associated with metabolic equivalents (METs) in a cohort of male patients. However, the prognostic implications of the HGI have never been externally validated with subgroup analyses based on gender, body mass index (BMI) of 35 kg/m^2, history of heart failure (HF), coronary artery disease (CAD) and beta-blocker use.

Methods: We identified 126,356 consecutive patients undergoing treadmill exercise testing between January 1st, 1991 and February 27th, 2015. HGI was calculated using the formula: $[(SBP_{peak} \times HR_{peak}) - (SBP_{rest} \times HR_{rest})] / (SBP_{rest} \times HR_{rest})$. Cox regression models were used to determine the associations between HGI quartiles and all-cause mortality with adjustment for cardiovascular risk factors and exercise testing parameters.

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CRediT authorship contribution statement

Thanat Chaikijurajai: Investigation, Writing- Original draft preparation. Wael Jaber: Data curation, Writing- Reviewing and Editing. Yuping Wu: Visualization, Methodology, Investigation. Serge Harb: Writing- Reviewing and Editing. Justin Grodin: Writing-Reviewing and Editing. W.H. Wilson Tang: Conceptualization, Supervision, Writing-Reviewing and Editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Tang is a consultant for Sequana Medical A.V., Cardiol Therapeutics Inc., Genomics plc, Zehna Therapeutics Inc., and has received honorarium from Springer Nature for authorship/editorship and American Board of Internal Medicine for exam writing committee participation - all unrelated to the subject and contents of this paper. Dr. Grodin is a consultant for Pfizer, Eidos, Alnylam, and Sarepta - all unrelated to the subject and contents of this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahjo.2022.100174.

Results: Mean age was 53.5 ± 12.6 years. There were 74,724 (59.1 %) male, 5940 (4.7 %) HF, 21,123 (16.7 %) CAD, and 30,568 (24.2 %) beta-blocker-using patients. During the median follow up of 7.1 years, 9929 (7.9 %) died. Median HGI was 1.93 (interquartile range [IQR] 1.40–2.54) bpm/mmHg. After adjustment for the covariates, lower HGI was independently associated with all-cause mortality in the entire cohort (quartile 1 vs 4, adjusted hazard ratio [95 % confidence interval] 1.33 [IQR 1.21–1.45], $p < 0.001$), and subgroups of men, women, patients with body mass index <35 kg/m^2, with and without HF, CAD, and beta-blocker use. The HGI also correlates well with METs in every subgroup.

Conclusions: The HGI is a strong predictor of long-term mortality independently of traditional cardiovascular risk factors, and exercise performance across patient subgroups.

Keywords

Hemodynamic gain index; Mortality; Heart failure; Coronary artery disease; beta-blocker

1. Introduction

Exercise stress testing is one of the most useful diagnostic and prognostic tools in patients with suspected or established cardiovascular disease [1–4]. Hemodynamic responses assessed by changes in blood pressure (BP) and heart rate (HR) during exercise testing provide invaluable information on the performance of cardiovascular system, functional capacity, cardiovascular risk factors, underlying cardiac and vascular dysfunction, and long-term prognosis [1,2,4–7]. For instance, a hypotensive response [8] and chronotropic incompetence [9,10] during exercise, as well as abnormal HR recovery (AHRR) [11–13] after exercise have been shown to be important prognostic markers independent of traditional cardiovascular risk factors. However, each measurement represents different components of the physiologic response of the systemic circulation to exercise at different time points, and, therefore, is not a comprehensive metric of the cardiovascular function under physical stress.

Recently, Vainshelboim et al. [14] developed a novel hemodynamic metric, the hemodynamic gain index (HGI), using the relative gain of the rate-pressure product (the product of HR and systolic BP [SBP]) from resting to peak values in a cohort of 11,455 men. They demonstrated that lower HGI was independently associated with a greater risk of all-cause mortality [14], and subsequently confirmed the findings in a smaller cohort of 606 women [15]. Nevertheless, the prognostic implications of the HGI have never been further externally validated with subgroup analyses based on sex, body mass index (BMI), the presence of heart failure (HF), coronary artery disease (CAD), and the use of beta-blockers, which may affect hemodynamic responses to exercise [1,4,16], and, potentially, the HGI [14]. Therefore, validating the prognostic significance of the HGI in a large cohort of men, women, patients with BMI ≥35 kg/m^2 and <35 kg/m^2, as well as patients with and without such cardiac conditions will provide more insights into the application of the HGI in clinical practice.

2. Methods

2.1. Study population

Data from the registry of consecutive patients referred for exercise stress testing for symptomatic evaluation were extracted and used in the analysis [17]. The detailed study design, methods, and baseline characteristics of the patients were previously published [17]. Briefly, the study cohort included 126,356 patients undergoing symptom-limited treadmill exercise stress testing from a registry of 166,447 patients who were referred for their first stress testing at the Cleveland Clinic from January 1st, 1991 to February 27th, 2015. We excluded patients who underwent pharmacologic stress tests (38,828 patients), were converted to pharmacologic stress test because of inability to reach desired HR (467 patients), and did not have sex information recorded (796 patients). Data on patient demographics, vital signs, medications, and comorbidities were collected at the time of the stress testing. HF was defined as presence of a clinical diagnosis of HF documented in the electronic medical record by the clinician. Patients who did not have HF information (24,692 patients) and could not be identified whether HF was presence or not, were excluded from the subgroup analysis on HF. CAD was defined as a previous history of myocardial infarction or coronary revascularization. The institutional review board approved the study with a waiver of the requirement for informed consent.

2.2. Exercise stress testing

The symptom-limited treadmill exercise stress testing was performed according to the standardized protocols and exercise testing guidelines [18]. Treadmill grade and speed at peak exercise were used to determine peak estimated metabolic equivalents (METs). AHRR was defined as HR reduction from peak HR to 1 min post exercise of ≤12 beats for a walking recovery, and ≤18 beats for a supine recovery [11,13,19]. Chronotropic reserve index (CRI) was calculated using the formula, $(HR_{peak} - HR_{rest})$ / (age-predicted $HR_{peak} - HR_{rest}$) [19].

2.3. Hemodynamic gain index

The HGI was calculated using the previously proposed formula, $[(HR_{peak} \times SBP_{peak}) - (HR_{rest} \times SBP_{rest})] / (HR_{rest} \times SBP_{rest})$ [14]. Our present study validated the prognostic value of the HGI stratified by quartiles and as a continuous value for all-cause mortality with adjustment for potential confounders.

2.4. Clinical outcomes

The primary outcome was all-cause mortality determined from the Social Security Death Index [20] and confirmed with chart documentation of patient's death (institutional death index) via electronic health records. The final censoring date was June 10, 2016.

2.5. Statistical analysis

Numeric data are presented as mean ± standard deviation. Categorical data are presented as n (%). One way ANOVA F test or Kruskal-Wallis test for continuous variables and $\chi 2$ test or Fisher Exact test for categorical variables were used to examine the difference between

groups. Hazard ratios for all-cause mortality at 10-year follow-up and corresponding 95 % confidence intervals were estimated using both univariable and multivariable Cox models adjusted for age, sex, the presence of CAD, diabetes, hypertension, dyslipidemia, chronic kidney disease, smoking history, BMI, CRI, ANHRR, METs, and total exercise time. Kaplan–Meier (KM) plots along with the log rank test were used to compare the estimated cumulative proportion of patients surviving over time. Spearman's correlation was used to determine if the HGI correlates with METs. In addition, discrimination analysis demonstrating the improvement in model performance introduced by the inclusion of HGI using net reclassification improvement (NRI) and area under the ROC curve (AUC) was also performed. *P*-values compared models with/without HGI. Both models were adjusted for previously known risk factors including age, sex, CAD, diabetics, HTN, hyperlipidemia, CKD, smoking, BMI, and ANHRR. The predicted probabilities of a Death event were estimated from the Cox model. All analyses were performed using R 4.0.4 (Vienna, Austria) and *p*-values <0.05 were considered statistically significant.

3. Results

A total of 126,356 patients underwent treadmill exercise stress testing. The mean age was 53.5 ± 12.6 years. There were 74,724 (59.1 %) male, 15,860 (12.6 %) with BMI ≥ 35 kg/m^2, 5940 (4.7 %) HF, 21,123 (16.7 %) CAD, and 30,568 (24.2 %) beta-blocker-using patients. During the median follow up of 7.1 years, 9929 (7.9 %) died. Mean HGI was 2.0 ± 1.2 bpm/mmHg in the entire cohort, 2.2 ± 1.1 bpm/mmHg in men, 1.8 ± 1.3 bpm/mmHg in women, 1.3 ± 0.8 bpm/mmHg in HF patients, 1.7 ± 1.0 bpm/mmHg in CAD patients, and 1.7 ± 1.0 bpm/mmHg in patients with beta blocker use. Patients with lower HGI were more likely to be older, female, smoker, have comorbidities (CAD, diabetes, hypertension, dyslipidemia, and chronic kidney disease), medication use (beta-blockers, non-dihydropyridine calcium channel blockers, statin, aspirin, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and insulin), lower METs and CRI, and higher prevalence of AHRR (Table 1). Even though the recruitment period lasted 24 years (1991 to 2015), average age of participants undergoing the test in each year was stable over time (Supplemental Fig. S1).

Table 2 shows the association between lower quartile of the HGI and all-cause mortality in the entire cohort. Lower quartile of the HGI was significantly associated with greater mortality (quartile 1 vs 4, hazard ratio 7.56, 95 % confidence interval [CI] 7.03–8.13; quartile 2 vs 4, hazard ratio 2.79, 95 % CI 2.58–3.02; quartile 3 vs 4, hazard ratio 1.63, 95 % CI 1.49–1.77; all $p < 0.001$), which remained statistically significant after adjustment for the covariates, except for quartile 3 vs 4 (quartile 1 vs 4, adjusted hazard ratio 1.33, 95 % CI 1.21–1.45, $p < 0.001$; quartile 2 vs 4, adjusted hazard ratio 1.14, 95 % CI 1.04–1.24, $p = 0.006$; quartile 3 vs 4, adjusted hazard ratio 1.03, 95 % CI 0.94–1.14; $p = 0.519$). The predictive value of the HGI for all-cause mortality was also significant over time when the analyses was performed in different groups of patients undergoing the test during 1991–1995, 1996–2000, 2001–2005, and 2006–2010, but not 2011–2014 when adjusted for the covariates (Supplemental Table S1). Moreover, for the continuous value of the HGI, higher HGI was independently associated with lower mortality (adjusted hazard ratio per standard deviation 0.84, 95 % CI 0.79–0.90, $p < 0.001$).

KM survival curves of patients stratified by HGI quartiles revealed that the divergence of all-cause mortality occurred among lower quartiles of the HGI in the entire cohort (log rank $p < 0.001$, Fig. 1) and every subgroup (all log rank $p < 0.001$) especially in patients with HF, CAD, and beta-blocker use, who had higher mortality rate. The associations between lower quartile of the HGI and all-cause mortality across subgroups are shown in Supplemental Table S2. The association between lower HGI and greater risk of all-cause mortality was consistent across subgroups of men, women, BMI < 35 kg/m^2, and patients with and without the history of HF, CAD, and beta-blocker use (p interaction ≤0.001 for all, Fig. 2, Supplemental Fig. S2). There was also a trend towards increasing morality with lower HGI in a subgroup of patients with BMI ≥ 35 kg/m^2 (adjusted hazard ratio 1.27, 95 % CI 0.99–1.62, $p = 0.058$, Fig. 2). Furthermore, in the entire cohort and subgroups of patients, the HGI correlated well with METs (all Spearman's correlation coefficients ≥0.49, all $p < 0.001$, Supplemental Table S3).

In the discrimination analysis, ROC curves of the risk prediction models using previously known risk factors including age, sex, CAD, diabetics, HTN, hyperlipidemia, CKD, smoking, BMI, and ANHRR with and without HGI were very similar (AUC of the model with HGI 0.82, 95 % CI 0.82–0.83, $p < 0.001$; AUC of the model without HGI 0.81, 95 % CI 0.81–0.82, $p < 0.001$). The NRI was 0.98 % in cases and 28.76 % in non-cases.

4. Discussion

In our present study, we demonstrated that lower HGI was independently associated with greater all-cause mortality risk after adjusting for cardiovascular risk factors and exercise testing parameters in a large cohort of patients undergoing treadmill exercise stress testing and subgroups of patients stratified by sex, BMI < 35 kg/m^2, history of HF, CAD, and beta blocker use. Despite the 24-year enrollment period, the independent association between HGI and all-cause mortality was significant over time, except for the last 5-year period. Our findings support the previous studies on the prognostic value of the HGI in two cohorts of men [14] and women [15], and validate the use of the HGI in patients regardless of the history of HF, CAD, and beta blocker use. In addition, HGI also significantly correlated with METs in the entire cohort and every subgroup. However, addition of HGI to the risk prediction model using traditional cardiovascular risk factors did not provide significant incremental value.

In the registry, even though the proportion of patients undergoing pharmacologic stress testing to those undergoing exercise or combined exercise/pharmacologic stress testing might seem low compared to other literature, our data were derived from all patients referred for their first treadmill exercise stress testing, which suggests that the study population was non-selective and represented the general population. Mean HGI in our subgroup of male patients (2.2 ± 1.1 bpm/mmHg) was higher than the original study of the HGI in men (1.68 ± 0.83 bpm/mmHg) [14], whereas less difference in mean HGI between our female cohort (1.8 ± 1.3 bpm/mmHg) and the subsequent female validation cohort (1.86 ± 0.82 bpm/mmHg) [15] was observed. The difference in the HGI between our cohort and the previous cohort of Veteran participants may be attributed to differences in the characteristics, given that our cohort included patients referred to an academic tertiary medical center.

The clinical significance of the HGI shown in our study was consistent with the original study, which demonstrated that patients with lower HGI were more likely to be older, have more comorbidities and medication use [14], thereby suggesting that the HGI might be a quantitative marker of health and functional status. In terms of prognostic implications, consistent with the previous studies [14,15], we confirmed that the association between HGI and all-cause mortality was consistent across the sexes. The impact of the HGI was also consistent over time, with the exception in patients undergoing the test during 2010–2014, which could attributed to the shorter follow-up period, and, therefore, lower event rate. We also validated and expanded the prognostic value of the HGI in subgroups of patients with BMI < 35 kg/m^2, and across the history of HF, CAD, and beta blocker use, which was previously suggested in the original study by the subgroup analyses on male patients with any cardiovascular disease and medications affecting hemodynamics [14].

Given that the HGI is derived from resting and peak HR and SBP, HGI may offer an integrated measurement of maximal hemodynamic response during exercise, which cannot be obtained from standard, single time-point parameters of exercise testing. Interestingly, the prognostic significance of the HGI was independent of parameters of heart rate response including CRI and ANHRR, which may indicate that change in BP is probably more influential than change in HR. Physiologically, the HGI was derived from the relative gain of the rate-pressure product (HR × SBP), a parameter that has been shown to indirectly reflect cardiovascular function and myocardial oxygen consumption [1,4,21,22]. Also, it is a comprehensive metric in which the rate-pressure product both at rest and peak exercise are taken into account in a single formula, which may offer additional value compared to the rate-pressure product measured at a single time point. Therefore, under physical stress, decreased HGI may suggest impaired cardiac, vascular compliance and performance attributed to cardiovascular risk factors, comorbidities, and disease. Furthermore, since the HGI is easily calculated, noninvasive, and readily available in treadmill exercise stress testing, it has potential to become an additional standard prognostic marker routinely measured for risk stratification, primary and secondary prevention.

In addition to validating the prognostic value of the HGI in the entire cohort, men, and women, we also aimed to demonstrate the prognostic significance of the HGI in subgroups of patients with and without certain conditions that may affect exercise performance and hemodynamic responses to exercise, such as significantly elevated BMI, HF, CAD, and beta blocker use [1,4,16]. Interestingly, the independent association between lower HGI and increased mortality remained robust in every subgroup of patients except for those with BMI ≥ 35 kg/m^2, in which a trend towards the similar finding was observed. This might be due to relatively smaller sample size compared to other subgroups, as well as the possibility that patients with significantly high BMI have limited exercise capacity, which the HGI might not be able to accurately reflect cardiovascular reserve function, thereby resulting in attenuated prognostic value of the HGI. Nevertheless, given the impact of HF, CAD, and beta-blocker use on hemodynamic responses and the HGI, different cutoff values and interpretation of the HGI for each group of patients may need to be applied in clinical practice.

Even though we demonstrated that the association between the HGI and all-cause mortality was statistically significant, and independent of traditional cardiovascular risk factors and exercise testing parameters, adding the HGI into the model failed to improve all-cause mortality risk discrimination. Given that the HGI reflects cardiovascular functional reserve, it is possible that the incremental value of the HGI may be limited to certain groups of patients who have significantly decreased cardiovascular fitness, such as HF. Therefore, the incremental value of the HGI remains to be elucidated.

The unique strength of our present study is that the prognostic significance of the HGI was validated in a large cohort of patients with a great mixture of demographics and medical conditions, as well as extended follow-up period (median duration 7.1 years). However, there are limitations that should be mentioned. Firstly, this is a single center study over an extended period of time with changes in medical therapy standards, and despite the large sample size that may overcome potential bias, these observations need to be further confirmed in other patient populations. Secondly, data on the history of HF (such as etiology, classification, functional class, left ventricular ejection fraction, and clinical stages) cannot be confirmed in all subjects retrospectively due to data missingness, and hence the clinical utility of the HGI remains to be elucidated in different subgroups of HF patients. We also do not have cardiopulmonary exercise parameters to confirm the relationship between HGI and peak oxygen consumption as external validation. Also, determination of HR in the setting of atrial fibrillation may vary as they were averaged when captured by the exercise testing equipment during the test protocol. Thirdly, given that Social Security Death Index only contains death data until March 2014, and death data from March 2014 to June 10, 2016 (final censoring date) were from institutional death index, it is likely that the event rate during that period of time was underestimated. Lastly, we primarily included variables based on prior studies on the prognostic value of the HGI and did not include all exercise parameters or other clinical, laboratory, imaging, and electrocardiographic variables that might be residual confounding factors were not included in the multivariable analysis.

5. Conclusions

In a large cohort of patients referred for treadmill exercise stress testing, we have validated that the HGI is independently associated with all-cause mortality after adjusted for cardiovascular risk factors and exercise performance in the entire cohort and across subgroups of patients stratified by sex, BMI, HF, CAD, and beta blocker use. Given that the HGI is a simple, noninvasive parameter that can be easily calculated from SBP and HR at resting and peak exercise, its clinical application as a novel prognostic tool in diverse patient populations is promising has the potential to increase the prognostic utility of treadmill exercise stress testing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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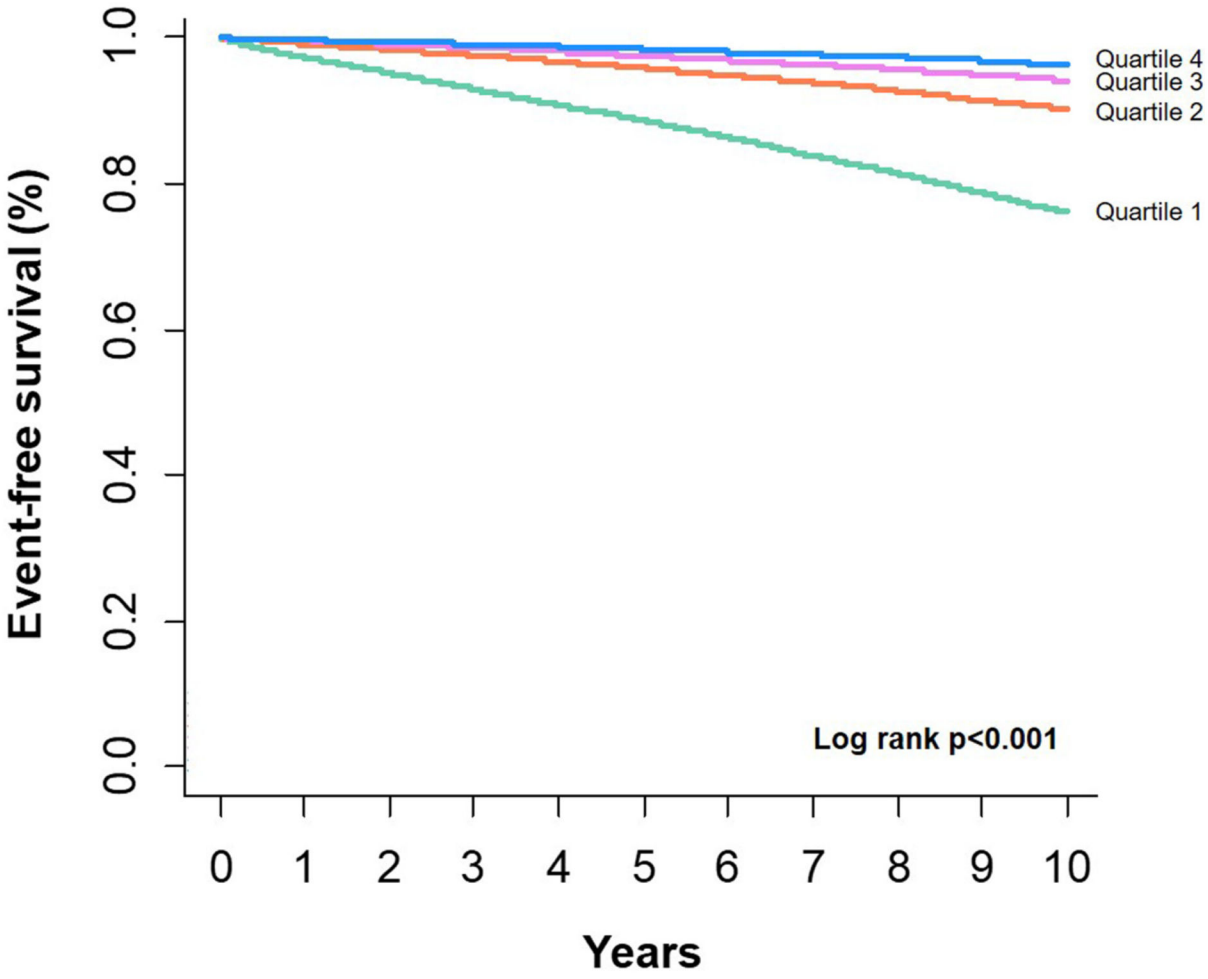

No. at risk											
Quartile 1	31128	29569	27278	24537	22070	19811	17801	15746	13946	12322	10711
Quartile 2	31127	30098	28921	26009	23793	21745	19780	17864	16040	14353	12651
Quartile 3	31127	30285	28631	26646	24724	22750	20898	19027	17197	15561	13827
Quartile 4	31128	30295	28897	27082	25264	23551	21918	20153	18349	16621	14853

Fig. 1.

Survival from all-cause mortality stratified by quartiles of the hemodynamic gain index of patients in the entire cohort.

Kaplan-Meier curves for survival from all-cause mortality based on quartiles of the hemodynamic gain index (HGI) in the entire cohort of 126,356 patients.

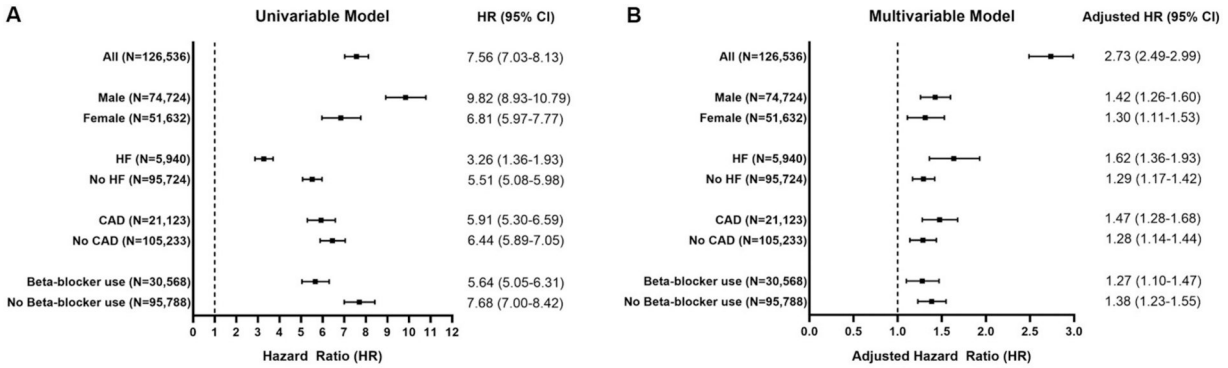

Fig. 2.

Forest plot for hazard ratio of all-cause mortality for hemodynamic gain index quartile 1 vs quartile 4 in the entire cohort and patient subgroups. Univariable (A) and multivariable (B) Cox proportional hazard models of hemodynamic gain index (HGI) quartile 1 compared to quartile 4 for all-cause mortality in the entire cohort and subgroups of men, women, patients with body mass index (BMI) ≥ 35 kg/m^2, <35 kg/m^2, and patients with and without heart failure (HF), coronary artery disease (CAD), and beta-blocker use.

Table 1

Baseline characteristic of the entire cohort based on quartiles of the hemodynamic gain index.

Variable	Hemodynamic gain index					
	All (*n* = 126,356)	**Quartile 1 (*n* = 31,128)**	**Quartile 2 (n = 31,127)**	**Quartile 3 (n = 31,127)**	**Quartile 4 (n = 31,128)**	***P* value**
Range (bpm/mmHg)		<1.40	1.40–1.93	1.93–2.54	≥2.54	
Age (years)	53.5 ± 12.6	59 ± 12.3	54.8 ± 12.2	51.8 ± 11.9	48.4 ± 11.5	<0.001
Male, n (%)	74,724 (59.1)	15,550 (50)	16,442 (52.8)	18,748 (60.2)	22,892 (73.5)	<0.001
Coronary artery disease, n (%)	21,123 (16.7)	8137 (26.1)	5222 (16.8)	4196 (13.5)	3405 (10.9)	<0.001
Diabetes, n (%)	14,806 (11.7)	6279 (20.2)	3900 (12.5)	2693 (8.7)	1716 (5.5)	<0.001
Hypertension, n (%)	68,550 (54.3)	23,377 (75.1)	18,413 (59.2)	14,988 (48.2)	10,950 (35.2)	<0.001
Hyperlipidemia, n (%)	19,313 (15.6)	6231 (20.3)	5201 (17)	4318 (14.1)	3503 (11.5)	<0.001
Smoker, n (%)	57,790 (45.7)	16,086 (51.7)	14,751 (47.4)	13,683 (44)	12,284 (39.5)	<0.001
Chronic kidney disease, n (%)	1451 (1.4)	840 (3.0)	291 (1.1)	172 (0.7)	130 (0.6)	<0.001
Body mass index (kg/m^2)	28.7 ± 5.8	29.5 ± 6.5	29.2 ± 6.1	28.6 ± 5.6	27.7 ± 4.9	<0.001
Resting systolic blood pressure (mmHg)	128.7 ± 19.1	135.8 ± 22.2	131.8 ± 18.3	127 ± 16.5	120.3 ± 15.2	<0.001
Resting heart rate (bpm)	72.9 ± 14	82.2 ± 16	75.9 ± 11.5	70.6 ± 10	62.5 ± 9.1	<0.001
Peak systolic blood pressure (mmHg)	175.3 ± 28.3	161.3 ± 28.6	173.8 ± 26.4	179.3 ± 26.1	186.6 ± 25.5	<0.001
Peak heart rate (bpm)	154.7 ± 22.6	137.4 ± 24.1	153.4 ± 18.6	160.6 ± 17.2	167.5 ± 17.7	<0.001
Peak metabolic equivalents	9.0 ± 2.8	6.8 ± 2.5	8.6 ± 2.2	9.6 ± 2.4	10.9 ± 2.3	<0.001
Abnormal heart rate recovery, n (%)	23,046 (18.2)	12,884 (41.4)	5300 (17)	2970 (9.5)	1709 (5.5)	<0.001
Chronotropic Reserve Index	0.88 ± 0.25	0.73 ± 0.38	0.88 ± 0.18	0.93 ± 0.15	0.97 ± 0.16	<0.001
Beta blocker use, n (%)	30,568 (24.2)	11,430 (36.7)	7866 (25.3)	6293 (20.2)	4711 (15.1)	<0.001
Non-dihydro calcium channel blocker use, n (%)	6301 (5.8)	2431 (8.3)	1690 (6.1)	1251 (4.8)	819 (3.4)	<0.001
Statin use, n (%)	32,743 (25.9)	10,569 (34)	8597 (27.6)	7239 (23.3)	6175 (19.8)	<0.001
Aspirin use, n (%)	41,919 (33.2)	12,415 (39.9)	10,756 (34.6)	9634 (31)	8703 (28)	<0.001
ACEi or ARB use, n (%)	30,814 (24.4)	11,409 (36.7)	8151 (26.2)	6284 (20.2)	4710 (15.1)	<0.001
Insulin use, n (%)	3855 (3.1)	1981 (6.4)	892 (2.9)	583 (1.9)	323 (1.0)	<0.001

Values are mean ± SD unless otherwise indicated. *P* values were from one way ANOVA F test or Kruskal-Wallis test for continuous variables and $\chi 2$ test or Fisher Exact test for categorical variables.

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; bpm = beats per minute.

Table 2

Hazard ratios for all-cause mortality per standard deviation increase and according to quartile of the hemodynamic gain index in the entire cohort.

HGI	Value or range (bpm/mmHg)	Total no. of patients	Event rate, n (%)	Univariate model			Adjusted model[a]		
				HR	95 % CI	p value	adjusted HR	95 % CI	P value
Per SD increase	1.20	126,356	9929 (7.9)	0.26	0.25–0.28	<0.001	0.84	0.79–0.90	<0.001
Quartile									
1	<1.40	31,128	5381 (17.29)	7.56	7.03–8.13	<0.001	1.33	1.21–1.45	<0.001
2	1.40–1.93	31,127	2158 (6.93)	2.79	2.58–3.02	<0.001	1.14	1.04–1.24	0.006
3	1.93–2.54	31,127	1308 (4.20)	1.63	1.49–1.77	<0.001	1.03	0.94–1.14	0.519
4 (referent)	≥2.54	31,128	833 (2.68)	1.00	–	–	1.00	–	–

Abbreviations: bpm = beats per minute; CI = confidence interval; HGI = hemodynamic gain index; HR = hazard ratio; SD = standard deviation.

[a]Adjusted model: age, gender, coronary artery disease, diabetes, hypertension, dyslipidemia, chronic kidney disease, smoking history, body mass index, chronotropic reserve index, abnormal heart rate recovery, peak metabolic equivalents, total exercise time.