# Incremental Prognostic Value of Exercise Stress Testing in Primary Prevention

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**In primary prevention, addition of C-reactive protein and family history to standard risk factor assessment (Reynolds Risk Score or RRS) provides superior risk stratification for future cardiovascular (CV) events. We sought to assess whether addition of functional capacity to RRS provided incremental prognostic value. This was a prospective observational cohort study of 3,964 consecutive asymptomatic adults without documented CV disease (mean age 51 years, 78% men) evaluated between 2005 and 2013, who underwent clinical and treadmill stress testing at baseline. RRS was calculated; % age-gender predicted metabolic equivalents (AGP-METs) achieved and heart rate recovery (HRR) were recorded. End point was death and myocardial infarction. Findings were tested in derivation (n = 1,982) and validation samples (n = 1,982). Mean RRS and C-reactive protein were 3.7 ± 4 and 2 ± 4 mg/dl. Nine percent had family history of premature CV disease. %AGP-METs achieved, and HRR were 113 ± 20 and 24 ± 8 beats/min. Forty-six percent achieved <110% AGP-METs, whereas 41% had RRS ≥3. At 7.3 ± 3 years, there were 83 (2%) events (39 in derivation and 44 in validation samples). In derivation group, on multivariable survival analysis, higher RRS (Hazard ratio or HR 1.27 [1.07 to 1.39]), lower % AGP METs (HR 1.21 [1.09 to 1.34]) achieved and abnormal (<12 beats/min) HRR (HR 1.15 [1.02 to 1.23]) were associated with increased longer-term events (all p <0.01). Findings were similar in validation group. Cutoffs of RRS >3 and %AGP-METs <110 were associated with increased longer-term events on spline analysis in the derivation group. The continuous net reclassification improvement for longer-term events, when %AGP-METs was added to RRS was 0.79 (95% confidence interval 0.52 to 1.05; p <0.01). Findings were confirmed in validation group. In conclusion, in primary prevention, addition of exercise capacity to RRS (incorporating traditional risk factors, family history, and inflammation) provides incremental prognostic value.**  **(Am J Cardiol 2019;124:216−223)**

In the last 50 years, significant improvements in atherosclerotic cardiovascular disease (ASCVD) mortality have occurred, in part due to development of multiple risk scores that allow better treatment of atherosclerotic risk factors and prediction of future cardiovascular (CV) events.[1−8] In addition to standard risk factors (as incorporated in ASCVD calculator),[4,6] family history of premature coronary heart disease (CHD) and inflammation are also crucial in prediction of future events. This has resulted in development of Reynolds Risk Score (RRS) which also identifies residual risk.[7,8] Additionally, reduced functional capacity has consistently been shown to be associated with worse outcomes in subjects at risk of CHD.[9−18] We hypothesized that the addition of exercise capacity to standard RRS (incorporating traditional risk factors, family history of premature CHD, and inflammation) would provide incremental prognostic value. The aims of the current study were to (1) test whether standard RRS and exercise capacity provide incremental and synergistic prognostic value for determining risk of developing future CHD in primary prevention, (2) derive thresholds beyond which abnormal RRS and impaired exercise capacity provide optimal reclassification of risk, and (3) validate the findings in an independent cohort.

## Methods

This was a prospective observational cohort study of 3,964 consecutive, asymptomatic subjects presenting for a comprehensive executive evaluation in the primary prevention clinic at our tertiary care center between January 2005 and December 2013. Participants were self-referred, and were evaluated in an outpatient ambulatory setting. All subjects were asymptomatic and free of documented ASCVD (including significant coronary artery disease, arrhythmic disease, peripheral arterial disease, cerebrovascular disease, aortic disease or valvular heart disease). No subject had a resting electrocardiographic abnormality (left bundle branch block, left ventricular hypertrophy with strain, digoxin therapy, pacemaker, pre-excitation or more than 1 mm of ST segment changes) that would preclude its interpretation. No

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subject had debilitating noncardiac diseases which could preclude a good exercise effort on the treadmill. The current registry was approved by the Institutional Review Board with waiver of individual informed consent.

Methods of prospective data collection in our stress test laboratory have been described in detail previously.[19–21] Before exercise stress testing, each patient participated in a structured history taking including documenting lack of symptoms, cardiac risk factors, family history of premature CHD, and medication use. Cholesterol and high-sensitivity C-reactive protein levels were obtained as part of a standard blood draw. We calculated ASCVD and standard RRS, as previously described.[4,6–8]

All patients underwent symptom-limited exercise treadmill testing primarily based on Bruce (n = 3,864, 97%) or modified Bruce protocols (n = 100, 3%).[22] Patients were instructed to hold their $\beta$-blockers 24 hours before the test. During each stage of exercise and for ≥6 minutes in recovery the following characteristics were recorded: symptoms, blood pressure, heart rate, cardiac rhythm, and exercise work load in metabolic equivalents (METs; 1 MET = 3.5 ml/kg per minute of oxygen consumption). We also calculated expected METs, based on age and gender, as previously described,[23] using the Veterans Affairs cohort formula (predicted METs = 18 − [0.15 × age]) and the St. James Take Heart Project formula (predicted METs = 14.7 − [0.13 × age]), for men and women, respectively. These formulae have been previously demonstrated to perform best in respective genders.[24] We subsequently calculated age-gender predicted METs (AGP-METs) as follows: (METS achieved/age-gender expected METS) × 100. We also calculated heart rate recovery (HRR) as the difference between heart rate at peak exercise and 1 minute later. Failure of the heart rate to decrease by more than 12 beats during the first minute following exercise constituted abnormal HRR.[20,21] Major (sustained ventricular or atrial arrhythmias associated with severe symptoms, hemodynamic compromise, or need for cardioversion) and minor events (decrease in blood pressure >20 mm Hg, transient symptoms, or nonsustained arrhythmias) were recorded. Duke treadmill score was calculated.[25]

The date of initial clinical evaluation at our center was defined as the beginning of the observation period. Patients were followed by chart review/follow-up visits and events/downstream cardiac procedures were recorded. Mortality data was obtained from review of medical records as well as state and nationally available databases (last query was November 2017). Nonfatal myocardial infarction (MI) was defined according to the 3rd universal definition.[26] We chose the composite primary end point of death or nonfatal MI. All-cause death was studied as a secondary end point. We also recorded percutaneous coronary intervention (PCI) and coronary artery bypass grafting in follow-up, along with stroke.

Using random number generation (between 0 and 1), equal derivation (those with random numbers ranging between 0 and 0.5, n = 1,982) and validation (those with random numbers >0.5 to 1, n = 1,982) groups were created. Comparative and survival analyses were performed separately in these groups. Continuous variables are expressed as mean ± standard deviation and/or median with interquartile range and compared using analysis of covariance or Mann-Whitney test, as appropriate. Categorical data is expressed as percentage and compared using chi-square. Spearman correlation coefficient was used to assess correlation between continuous variables. To assess longer-term outcomes, univariable and multivariable Cox proportional hazards analysis was performed separately in derivation and validation subgroups, incorporating relevant predictors known to be associated with longer-term adverse events in this population. Hazard ratios (HR) with 95% confidence intervals (CI) were calculated. Also, in the derivation cohort, the functional relation between RRS, %AGP-METs and risk of composite events was assessed using penalized splines to estimate hazards in a Cox model. Relation between exposure and response were described with the fitted splines and standard error bars with HR on the Y-axis and exposure on the X-axis. Using the splines, we estimated the appropriate cutoff of continuous variable (RRS or %AGP-METs) associated with increased composite events (where the HR of 1 was crossed). Using these cutoffs, cumulative proportion of patients with composite events as a function over time was obtained by Kaplan-Meier method and compared using log-rank test. In addition, the incremental prognostic utility of the various models was tested using log-likelihood ratios, reclassification of risk of composite events using integrated discrimination improvement (IDI) and net reclassification improvement (NRI). Since longer-term death and nonfatal MI were competing risks, multivariable survival analysis (for the outcome of death) was performed by competing risk regression analysis using the Fine-Gray proportional subhazards model, and subdistribution hazard ratios (sHR) were calculated. Statistical analysis was performed using SPSS version 11.5 (SPSS Inc., Chicago, Illinois) and R 3.4.3 (R foundation, Vienna, Austria). A p value of <0.05 was considered significant.

## Results

The clinical and treadmill stress data are shown in Tables 1 and 2. There were no significant differences in various parameters between derivation and validation groups. There was no significant correlation between RRS and % AGP-METs in both, derivation (r = −0.02, p = 0.28) and validation (r = −0.03, p = 0.17) groups, respectively.

At a mean follow-up of 7.3 ± 3 years (median 7.7 years [interquartile range 4.9 to 9.8]), there were 83 (2%) composite events (39 in derivation and 44 in validation groups, respectively). Of these, there were 45 (1%) deaths (24 in derivation and 21 in validation groups, respectively) and 38 nonfatal MI (15 in derivation and 23 in validation groups, respectively). A total of 49 patients underwent PCI (including 38 primary PCI, following MI), whereas 10 underwent coronary artery bypass grafting during follow-up (no differences between derivation and validation groups). Stroke was observed in 9 (0.2%) patients (no differences between derivation and validation groups).

The results of univariable Cox Proportional Hazard analysis, for derivation and validation groups, are shown in Supplemental Table 1. The results of multivariable Cox Proportional Hazard analysis, for derivation and validation groups, are shown in Table 3.

Table 1
Baseline demographic and clinical data in the study cohort as a whole and divided into derivation and validation groups

| Variable | Total study sample (n = 3,964) | Derivation cohort (n = 1,982) | Validation cohort (n = 1,982) | p Value |
|---|---|---|---|---|
| Age (years) | 51 ± 8 | 51 ± 8 | 51 ± 8 | 0.15 |
| Men | 3,106 (78%) | 1,536 (78%) | 1,570 (79%) | 0.10 |
| Body mass index (kg/m$^2$) | 28 ± 5 | 28 ± 5 | 28 ± 5 | 0.43 |
| Family history of premature CHD | 366 (9%) | 183 (9%) | 183 (9%) | 0.52 |
| Hypertension | 563 (14%) | 274 (14%) | 289 (15%) | 0.26 |
| Diabetes mellitus | 121 (3%) | 61 (3%) | 60 (3%) | 0.50 |
| Hyperlipidemia | 1,496 (38%) | 764 (39%) | 732 (37%) | 0.16 |
| Smoker | 513 (13%) | 258 (13%) | 255 (13%) | 0.46 |
| Lone atrial fibrillation | 15 (0.4%) | 6 (0.3%) | 9 (0.5%) | 0.30 |
| Betablockers | 169 (4%) | 82 (4%) | 87 (4%) | 0.38 |
| ACE-inhibitors or ARBs | 478 (12%) | 236 (12%) | 242 (12%) | 0.77 |
| Calcium channel blockers | 132 (3%) | 74 (4%) | 58 (3%) | 0.09 |
| Diuretics | 307 (8%) | 158 (8%) | 149 (8%) | 0.32 |
| Statins | 835 (21%) | 414 (21%) | 421 (21%) | 0.41 |
| Aspirin | 818 (21%) | 423 (21%) | 395 (20%) | 0.15 |
| Anticoagulants | 15 (0.4%) | 6 (0.3%) | 9 (0.5%) | 0.30 |
| Hemoglobin (mg/dl) | 14.8 ± 1 | 14.8 ± 1 | 14.8 ± 1 | 0.41 |
| Hematocrit (mg/dl) | 44 ± 3 | 44 ± 3 | 44 ± 3 | 0.41 |
| Serum creatinine (mg/dl) | 0.9 ± 0.2 | 0.9 ± 0.2 | 0.9 ± 2 | 0.23 |
| Total cholesterol (mg/dl) | 197 ± 37 | 197 ± 36 | 196 ± 38 | 0.15 |
| High density lipoprotein (mg/dl) | 57 ± 17 | 57 ± 17 | 56 ± 14 | 0.12 |
| Low density lipoprotein (mg/dl) | 116 ± 33 | 115 ± 33 | 116 ± 33 | 0.32 |
| Triglycerides (mg/dl) | 123 ± 78 | 122 ± 84 | 124 ± 79 | 0.23 |
| Ultrasensitive CRP (mg/dl) | 2.02 ± 4 | 2.05 ± 4 | 2.01 ± 0.4 | 0.75 |
| Reynolds risk score | 3.7 ± 4 | 3.8 ± 4 | 3.7 ± 4 | 0.38 |
| Reynolds risk score | | | | |
| <3 | 2,322 (59%) | 1,179 (60%) | 1,143 (58%) | 0.58 |
| ≥3 | 1,642 (41%) | 803 (40%) | 839 (42%) | |
| ASCVD risk score | 4.9 ± 6 | 5.0 ± 6 | 4.9 ± 6 | 0.41 |

CHD = coronary heart disease; ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; CRP = c-reactive protein; ASCVD = atherosclerotic cardiovascular disease.

p Values reflect differences between derivation and validation groups.

Addition of %AGP-METs to RRS provided incremental prognostic utility and reclassified risk of composite events in derivation and validation groups. In the derivation group, the IDI and continuous NRI for longer-term events, when %AGP-METs was added to RRS were (0.017 [95% CI 0.004 to 0.0306] and 0.79 [95% CI 0.52 to 0.95], both $p < 0.01$), respectively. Also, addition of %AGP-METs to RRS significantly improved the LLR from −252.26 to −245.13 (Chi-square 13, $p < 0.001$). Similarly, in the validation group, the IDI and continuous NRI for longer-term events, when %AGP-METs was added to RRS were (0.006 [95% CI 0.003 to 0.01 and 0.56 [95% CI 0.28 to 0.83], both $p < 0.01$), respectively. Also, addition of %AGP-METs to RRS significantly improved the LLR from −291.70 to −286.89 (Chi-square 10, $p = 0.002$). Additional data for IDI and NRI are shown in Supplemental Table 2).

Subsequently, in the derivation group, we performed spline analysis, as shown in Figure 1. Based on the spline analysis, in the present study, AGP-METs <110% (Figure 1) and RRS ≥3 (Figure 1) were deemed optimal cut-offs that were associated with an increased frequency of composite events. Based on these cutoffs, we performed subsequent Kaplan-Meier survival analysis in the derivation and validation groups. Within the derivation group, the proportion of longer-term composite events was significantly higher in the subgroup of subjects with low versus high AGP-METs: [32/915 (3.5%) vs 7/1067 (0.7%), $p < 0.001$, Figure 2). Also, the proportion of longer-term composite events was significantly higher in the subgroup of subjects with high versus low RRS: [29/803 (3.6%) vs 10/1179 (0.8%), $p < 0.001$, Figure 2). We subsequently divided the derivation group into 2 subgroups, as follows: A) Both, RRS <3 and %AGP-METs ≥110% and B) Either RRS ≥3 and/or %AGP-METs <110. The proportion of longer-term composite events were significantly lower in the subgroup A versus subgroup B [2/659 (0.3%) vs 37/1323 (2.8%), $p < 0.001$, Supplemental Figure 1).

We performed similar analysis in the validation group, based on RRS and AGP-METs cutoffs obtained in the derivation group above. The proportion of composite events were significantly higher in the subgroup of subjects with low versus high AGP-METs [32/891 (3.6%) vs 12/1091 (1.1%), $p < 0.001$, Figure 2). Also, the proportion of composite events were significantly higher in the subgroup of subjects with high versus low RRS [32/839 (3.8%) vs 12/1143 (1%), $p < 0.001$, Figure 2). We also divided the validation group into 2 subgroups, as follows: A) Both, RRS <3 and %AGP-METs ≥110% and B) Either RRS ≥3 and/or %AGP-METs <110. The proportion of longer-term composite events were significantly lower in the subgroup A versus subgroup B [4/644 (0.6%) vs 40/1338 (3%), $p = 0.001$, Supplemental Figure 2).

Table 2
Baseline treadmill stress testing data in the study cohort as a whole and divided into derivation and validation groups

| Variable | Total study sample (n = 3,964) | Derivation cohort (n = 1,982) | Validation cohort (n = 1,982) | p Value |
|---|---|---|---|---|
| Resting HR (beats/minute) | 68 ± 7 | 68 ± 6 | 68 ± 7 | 0.72 |
| Resting systolic BP (mm Hg) | 123 ± 15 | 123 ± 15 | 123 ± 15 | 0.75 |
| Resting diastolic BP (mm Hg) | 81 ± 9 | 81 ± 9 | 81 ± 9 | 0.80 |
| Peak HR (beats/minute) | 165 ± 14 | 165 ± 14 | 165 ± 14 | 0.21 |
| Peak systolic BP (mm Hg) | 179 ± 25 | 179 ± 26 | 179 ± 24 | 0.71 |
| Peak diastolic BP (mm Hg) | 87 ± 11 | 87 ± 11 | 87 ± 11 | 0.99 |
| Peak rate pressure product | 29582 ± 4731 | 29,660 ± 4,854 | 29,503 ± 4,604 | 0.30 |
| Total exercise time (seconds) | 607 ± 126 | 605 ± 126 | 609 ± 125 | 0.38 |
| METs achieved | 11 ± 2 | 11 ± 2 | 11 ± 2 | 0.46 |
| % AGP-METs achieved | 113 ± 20 | 113 ± 20 | 113 ± 20 | 0.44 |
| AGP-METs achieved | | | | |
| *110%* | 2,158 (54%) | 1,067 (54%) | 1,091 (55%) | 0.79 |
| *<110%* | 1,806 (46%) | 915 (46%) | 891 (45%) | |
| HRR (beats/minute) | 24 ± 9 | 24 ± 9 | 24 ± 9 | 0.89 |
| Abnormal HRR | 273 (7%) | 137 (7%) | 136 (7%) | 0.95 |
| % PMHR | 97 ± 7 | 97 ± 7 | 97 ± 7 | 0.38 |
| Reason to terminate the stress test | | | | |
| *Fatigue* | 3,948 (99%) | 1,974 (99%) | 1,972 (99%) | |
| *Chest pain* | 3 (0.1%) | 1 (0.1%) | 2 (0.1%) | 0.89 |
| *Abnormal systolic BP drop (>20 mm Hg) at peak stress* | 13 (0.3%) | 7 (0.4%) | 6 (0.3%) | |
| Abnormal ECG at peak stress | | | | |
| *Downsloping ST depression* | 184 (5%) | 97 (5%) | 81 (4%) | 0.25 |
| *Upsloping ST depression* | 110 (3%) | 52 (3%) | 58 (3%) | 0.31 |
| *Rapidly resolved ST depression in recovery* | 266 (7%) | 136 (7%) | 140 (7%) | 0.80 |
| Arrhythmias during stress testing | | | | |
| *PVC's* | 20 (0.5%) | 6 (0.3%) | 14 (0.7%) | 0.06 |
| *Nonsustained VT* | 8 (0.2%) | 5 (0.3%) | 3 (0.2%) | 0.36 |
| *Atrial fibrillation* | 1 (0.1%) | 1 (0.1%) | 0 | 0.50 |
| *LBBB* | 1 (0.1%) | 0 | 1 (0.1%) | 0.50 |
| Duke treadmill score | | | | |
| *Normal ( 5)* | 3,797 (96%) | 1,892 (95%) | 1,905 (96%) | |
| *Intermediate (between 5 and −10)* | 167 (4%) | 90 (5%) | 77 (4%) | 0.30 |
| *Very abnormal (worse than −10)* | 0 | 0 | 0 | |

HR = heart rate; BP = blood pressure; AGP-METs = age-gender predicted metabolic equivalents; HRR = heart rate recovery; ECG = electrocardiogram; PVC = premature ventricular contraction; VT = ventricular tachycardia; LBBB = left bundle branch block.
p Values reflect differences between derivation and validation groups.

Using the cutoffs for RRS and %AGP-METs, we also demonstrate that addition of %AGP-METs to RRS provides incremental reclassification of risk for composite events. In the derivation group (Figure 3), 74% subjects with composite events had high RRS; when AGP-METs <110% was incorporated into risk calculation, 95% subjects with subsequent events had high RRS and low %AGP-METs. Similarly, in the validation group (Figure 3), 73% subjects with composite

Table 3
Multivariable Cox Proportional Hazard Survival analysis in the study cohort (for the composite outcome of death and nonfatal myocardial infarction) divided into derivation and validation groups

| Variable | Hazard ratio (95% Confidence Interval) | p Value |
|---|---|---|
| *Derivation cohort (n = 1,982, number of composite events = 39)* | | |
| Reynolds risk score | 1.13 [1.09-1.18] | <0.001 |
| % Age-gender predicted metabolic equivalents (for every 10% decrease) | 1.27 [1.11-1.46] | 0.001 |
| Abnormal heart rate recovery at 1 minute in recovery | 1.99 [1.42-6.28] | 0.003 |
| Statin use | 0.59 [0.42-1.13] | 0.21 |
| *Validation cohort (n = 1,982, number of composite events = 44)* | | |
| Reynolds risk score | 1.10 [1.06-1.15] | <0.001 |
| % Age-gender predicted metabolic equivalents (for every 10% decrease) | 1.22 [1.04-1.23] | 0.009 |
| Abnormal heart rate recovery at 1 minute in recovery | 2.41 [1.05-5.51] | 0.03 |
| Statin use | 0.64 [0.38-1.20] | 0.33 |

Variables with $p < 0.1$ on univariable analyses were considered for multivariable analyses.
Findings were similar if atherosclerotic cardiovascular disease risk score was substituted for Reynolds risk score.

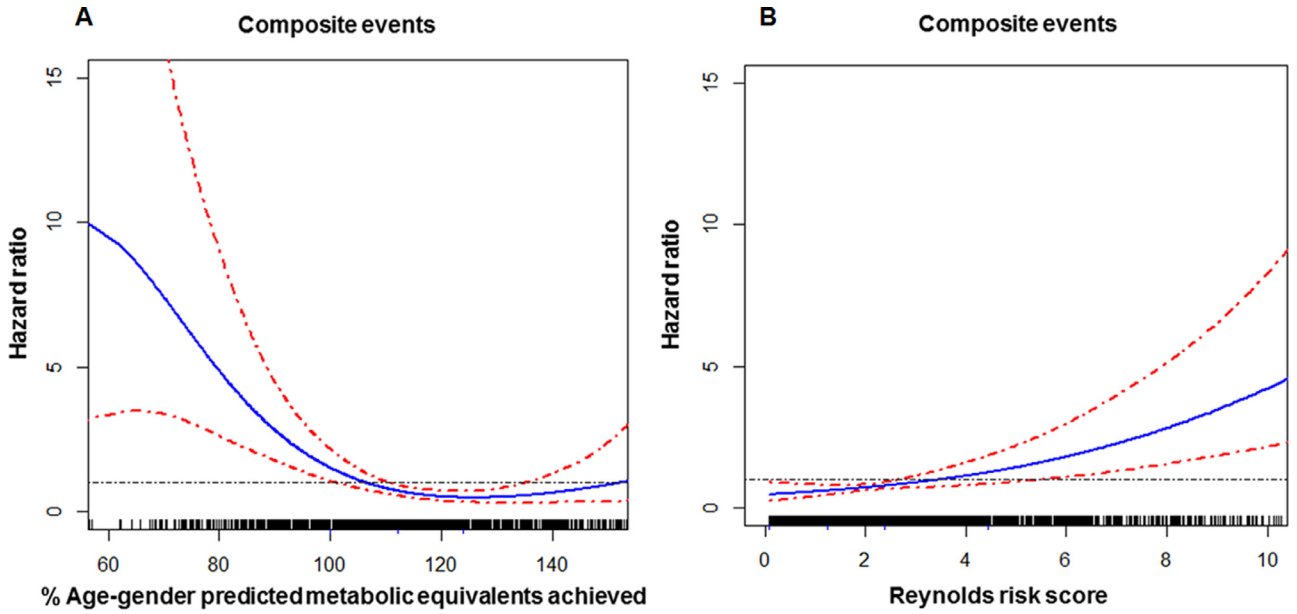


Figure 1. Penalized spline analysis in the derivation group testing the functional relationship between (*A*) % age-gender predicted metabolic equivalents achieved (AGP-METs), (*B*) Reynolds risk score (RRS) and risk of composite events in a Cox model. Abnormal cutoff was assumed where the hazard ratio of 1 was crossed.

events had high RRS; when AGP-METs <110% was incorporated into risk calculation, 91% subjects with subsequent events had high RRS and low %AGP-METs.

Association between RRS, %AGP-METs and the secondary outcome of death was tested using competing risk survival analysis, separately in derivation and validation groups. In the derivation group (number of deaths = 24), on multivariable competing risk analysis, both RRS (sHR 1.12 [95% CI 1.07 to 1.18], $p < 0.001$) and % AGP-METs (for every 10% decrease sHR 1.36 [95% CI 1.16 to 1.60], $p < 0.001$) were independently associated with longer-term death. Similarly, in the validation group (number of deaths = 21), both RRS (sHR 1.09 [95% CI 1.03 to 1.16], $p = 0.009$) and % AGP-METs (for every 10% decrease sHR 1.35 [95% CI 1.11 to 1.65], $p < 0.001$) were also independently associated with longer-term death.

## Discussion

In this large cohort of 3,964 consecutive asymptomatic low risk subjects (majority of whom were free of traditional risk factors) undergoing a comprehensive executive health evaluation, we demonstrate that addition of %AGP-METs to RRS provided incremental and synergistic value. These findings were consistent and present in both the validation as well as the derivation cohorts. For baseline assessment for future CHD risk, we predominantly focused on RRS, as it combines measurement of traditional risk factors, family history of premature CHD and inflammation. However, the findings were similar, if standard ASCVD risk calculator was substituted for RRS. The incremental value of functional capacity is especially noteworthy in that our cohort comprised of an asymptomatic, low risk subjects as opposed to population groups with preponderance of risk factors and higher likelihood of CHD. Also, for continuous variables like RRS and %AGP-METs, rather than using arbitrary cutoffs, we performed spline analysis which demonstrated that, in our derivation cohort, RRS <3 and %AGP-METs >110% were associated with significantly improved longer-term freedom from composite events.

Although previous studies on exercise stress testing have focused on patients with (or at-risk of) documented CHD,[9–18] the value of exercise stress testing for CV screening in asymptomatic individuals remains in question, in large part because of the poor accuracy of ST-segment changes for diagnosing coronary artery disease. As a result, previous studies have focused on other measures that have far greater prognostic value, particularly exercise capacity and HRR.[19–21] In the present study, there was no association of Duke treadmill score (which incorporates ST segment changes) and outcomes, whereas exercise capacity and HRR were predictive. One of the potential reasons for Duke treadmill score[25] and ST segments[27] not being predictive is because this study was performed in asymptomatic, low risk individuals as opposed to other cohorts (for instance, 67% of patients in the Duke treadmill s0core derivation study had stable angina, whereas 33% had progressive angina[25]).

Indeed, previous studies have demonstrated incremental utility of exercise capacity in addition to traditional risk factor assessment in asymptomatic individuals.[17–19] However, unlike in the previous reports, we calculated %AGP-METs achieved in every individual.[24] Furthermore, we derived an optimal threshold of 110% of AGP-METs achieved which best aided in incremental prognostication in our cohort, which was subsequently validated in a separate cohort. Given the fact that ours was a low-risk asymptomatic cohort (and these formulae were developed in predominantly symptomatic individuals), it makes intuitive sense that the cutoff of AGP-METs which best distinguishes at-risk individuals is supranormal (i.e., 110%).

Another important distinction is the utilization of standard RRS, which takes into account traditional CHD risk factors,

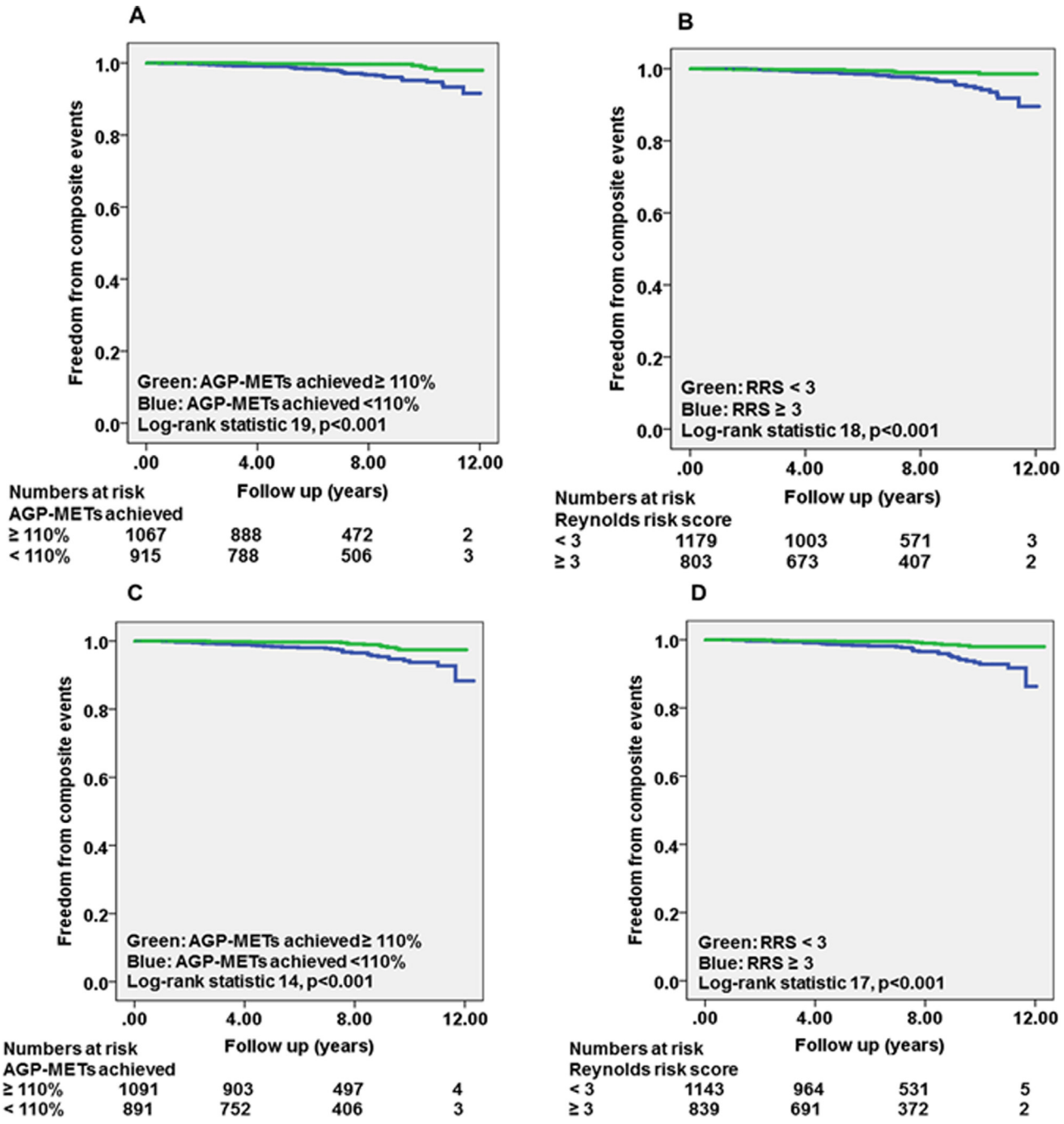


Figure 2. Kaplan-Meier survival curves separated based on (*A*) achieving 110% of AGP-METs (derivation group) (*B*) RRS cutoff of 3 (derivation group) (*C*) achieving 110% of AGP-METs (validation group) (*D*) RRS cutoff of 3 (validation group). Cutoff values for RRS and AGP-METs derived from Figure 1.

family history and inflammation.[7,8,28] Using RRS significantly reduces residual risk and improves ascertainment of future risk of CHD. We also demonstrate that RRS ≥3 best aided in incremental prognostication. Although one could argue about the necessity of additional risk stratification beyond traditional risk factor assessment, family history of premature CHD and inflammation [provided by RRS (Figure 3)], even RRS resulted in residual risk of a future CHD; and addition of AGP-METs further improved risk stratification. However, currently, United States Preventive Services Task Force does not recommend exercise stress testing (or addition of nontraditional risk factors like C-reactive protein or calcium scoring) in asymptomatic low-risk individuals.[29] But addition of functional capacity provides incremental value in predicting the risk of CV events beyond the conventional risk factors/inflammation and maybe used by clinicians to assess the risk of future CHD event and potentially allow to counsel the patients in maintaining an active lifestyle and in promotion of exercise.

This is an observational study from a large tertiary care center with its inherent biases. The study cohort came from an executive health clinic, the majority of whom were men,

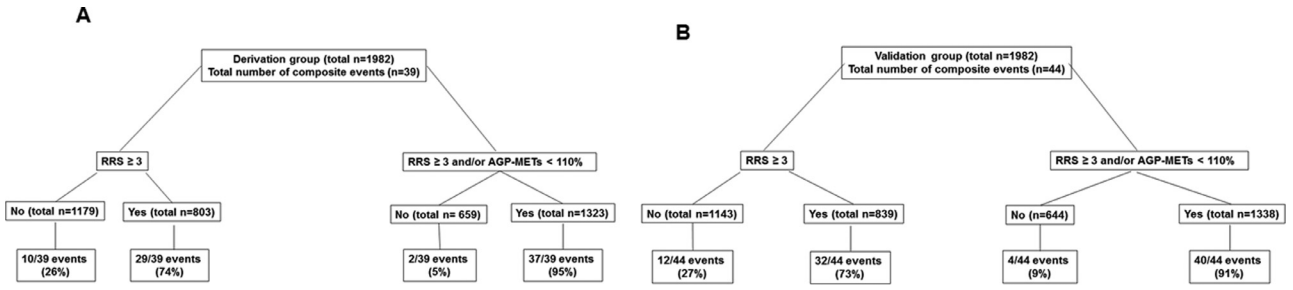


Figure 3. Incremental reclassification of risk for composite events addition of %AGP-METs to RRS in the (*A*) derivation group and (*B*) validation group.

and it is likely that our patients likely had ready access to health care, a higher socioeconomic status, and a high level of interest in maintaining long-term health. Whether our results may be generalized to other populations will require further study. The present study reports associations and does not report causality. There could be additional potential confounders that were not accounted for; and given the low number of events, the present study could also be potentially underpowered. Coronary calcium scoring was not routinely performed in this population at the time; hence the data is not reported. There is the potential for an increase in downstream costs related to unnecessary testing and harm from unnecessary invasive procedures associated with screening programs. However, the results could help guide physicians to manage higher-risk individuals with aggressive primary prevention strategies, including medications, exercise, weight loss, and risk factor/stress control. Finally, we report all-cause mortality as it is less prone to bias.

In a group of consecutive asymptomatic subjects without documented CV disease undergoing comprehensive screening for primary prevention, we demonstrate that, in addition to detecting abnormal exercise response, assessment of exercise capacity to standard RRS (incorporating traditional risk factors, family history of premature CHD and inflammation) provides incremental prognostic value for future CHD-related events. In asymptomatic low-risk individuals, addition of functional capacity could potentially help guide higher-risk individuals with more aggressive primary prevention strategies, including medical therapy, exercise prescription, weight loss prescription and risk factor/stress control. These findings need to be validated in a multicenter cohort.

## Disclosures

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## Supplementary materials

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