

ONLINE SUPPLEMENT

A Biomarker-Based Risk Score for Predicting Hospitalization for Heart Failure in Patients with Diabetes

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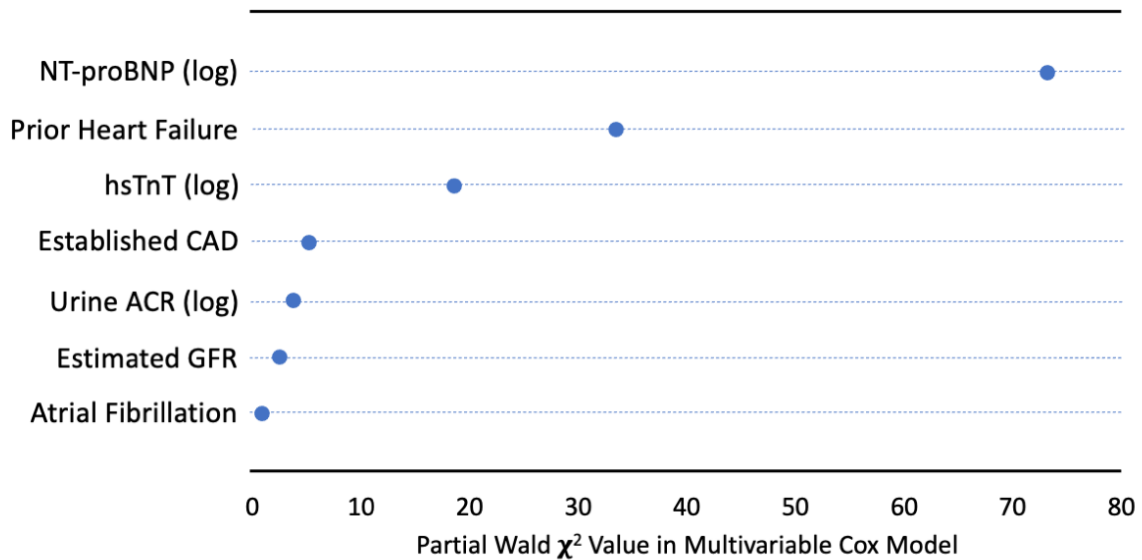
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Supplemental Table 1. Baseline characteristics by established biomarker categories in the validation cohort. Categorical variables are shown as counts and percentages; continuous variables are shown as medians with 25th-75th percentiles. Differences in baseline characteristics between biomarker strata were evaluated with the Pearson chi-squared test for categorical variables and Kruskal-Wallis test for continuous variables. eGFR, estimated glomerular filtration rate; g, gram; hsTnT, high-sensitivity troponin T; IQR, interquartile range; min, mg, milligram, minute; ml, milliliter; mmHg, millimeters of mercury; NT-proBNP, N-terminal pro-B type natriuretic peptide.

| Variable | hsTnT (ng/L) | | | | | NT-proBNP (pg/ml) | | | | |
|--|------------------|-------------------|--------------------|------------------|---------|-------------------|---------------------|----------------------|-------------------|---------|
| | <6 (N=1321) | 6-<10 (N=2180) | 10-<14 (N=1573) | ≥14 (N=2177) | P-value | <50 (N=2601) | 50-<125 (N=2270) | 125-<450 (N=1757) | ≥450 (N=623) | P-value |
| <i>Demographics</i> | | | | | | | | | | |
| Age, median (25 th -75 th), years | 62 (59-66) | 63 (59-67) | 64 (60-69) | 65 (61-70) | <0.001 | 62 (58-66) | 64 (60-69) | 66 (61-70) | 66 (61-71) | <0.001 |
| Female sex | 904 (68.4) | 955 (43.8) | 466 (29.6) | 408 (18.7) | <0.001 | 858 (33.0) | 946 (41.7) | 733 (41.7) | 196 (31.5) | <0.001 |
| White race | 960 (72.7) | 1720 (78.9) | 1299 (82.6) | 1892 (86.9) | <0.001 | 1975 (75.9) | 1846 (81.3) | 1491 (84.9) | 559 (89.7) | <0.001 |
| Body-mass index, median (25 th -75 th), kg/m ² | 30.4 (27.1-34.3) | 30.9 (27.7-34.9) | 31.9 (28.1-35.7) | 32.3 (28.6-36.4) | <0.001 | 31.1 (27.6-35.1) | 31.5 (28.0-35.5) | 31.9 (28.0-35.8) | 31.9 (28.3-36.4) | 0.001 |
| | | | | | | | | | | |
| <i>Diabetes History</i> | | | | | | | | | | |
| Duration of type 2 diabetes, median (IQR), years | 9.0 (5.0-14.0) | 10.0 (6.0-15.0) | 11.0 (6.0-16.0) | 12.0 (7.0-19.0) | <0.001 | 10.0 (6.0-15.0) | 11.0 (6.0-16.0) | 12.0 (7.0-18.0) | 11.0 (6.0-18.0) | <0.001 |
| Hemoglobin A1c, median (25 th -75 th), % | 7.9 (7.3-8.9) | 8.0 (7.3-8.9) | 8.0 (7.3-8.9) | 8.1 (7.4-9.1) | <0.001 | 8.0 (7.4-9.0) | 8.0 (7.3-8.9) | 8.0 (7.3-8.9) | 8.0 (7.3-9.0) | 0.208 |
| Baseline insulin use | 394 (29.8) | 759 (34.8) | 668 (42.5) | 1142 (52.5) | <0.001 | 1008 (38.8) | 885 (39.0) | 790 (45.0) | 280 (44.9) | <0.001 |
| Diabetic retinopathy | 119 (9.4) | 216 (10.2) | 210 (13.8) | 371 (17.7) | <0.001 | 277 (10.9) | 275 (12.6) | 269 (15.9) | 95 (16.1) | <0.001 |
| Diabetic nephropathy | 43 (3.3) | 127 (5.9) | 136 (8.8) | 267 (12.5) | <0.001 | 180 (7.0) | 163 (7.3) | 172 (10.0) | 58 (9.6) | 0.001 |
| eGFR, median (25 th -75 th), ml/min/1.73 m ² | 95 (87-101) | 91 (79-98) | 86 (73-95) | 81 (66-92) | <0.001 | 92 (81-99) | 88 (75-96) | 85 (71-94) | 77 (62-89) | <0.001 |
| Urine albumin-to-creatinine ratio (UACR), median (25 th -75 th), mg/g | 9.3 (5.0-21.3) | 11.0 (5.5-28.3) | 13.3 (6.0-44.2) | 21.7 (7.8-96.6) | <0.001 | 10.2 (5.2-26.9) | 12.0 (5.7-35.4) | 17.8 (7.2-67.5) | 34.1 (10.7-160.8) | <0.001 |
| | | | | | | | | | | |
| <i>Other Comorbidities</i> | | | | | | | | | | |
| Coronary artery disease | 300 (22.7) | 634 (29.1) | 552 (35.1) | 954 (43.8) | <0.001 | 582 (22.4) | 715 (31.5) | 799 (45.5) | 344 (55.2) | <0.001 |

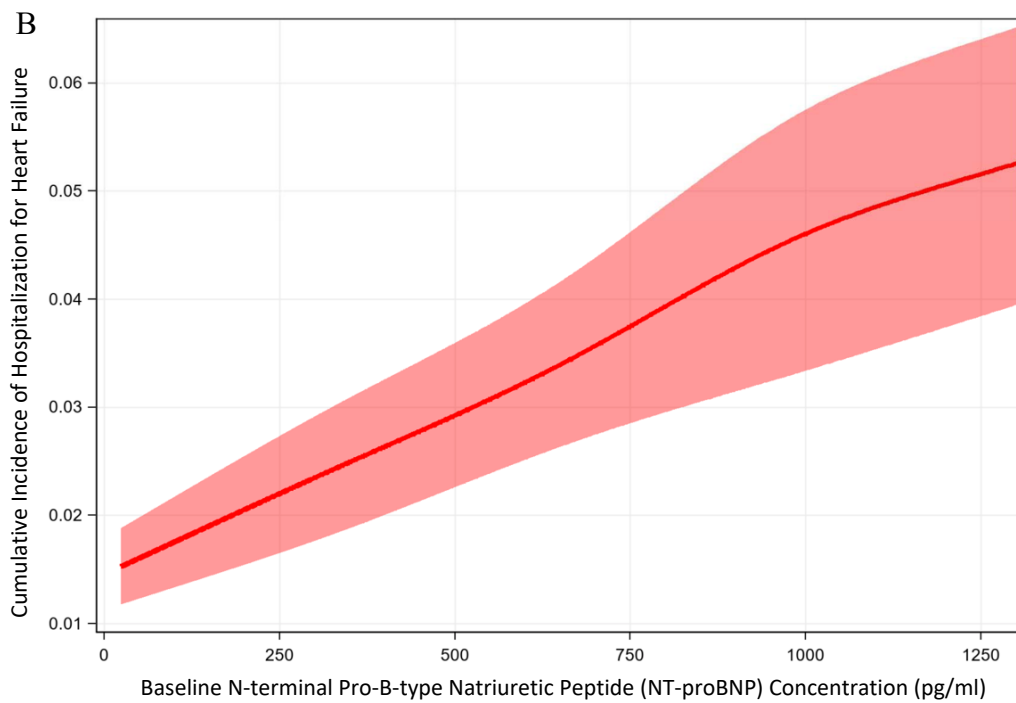
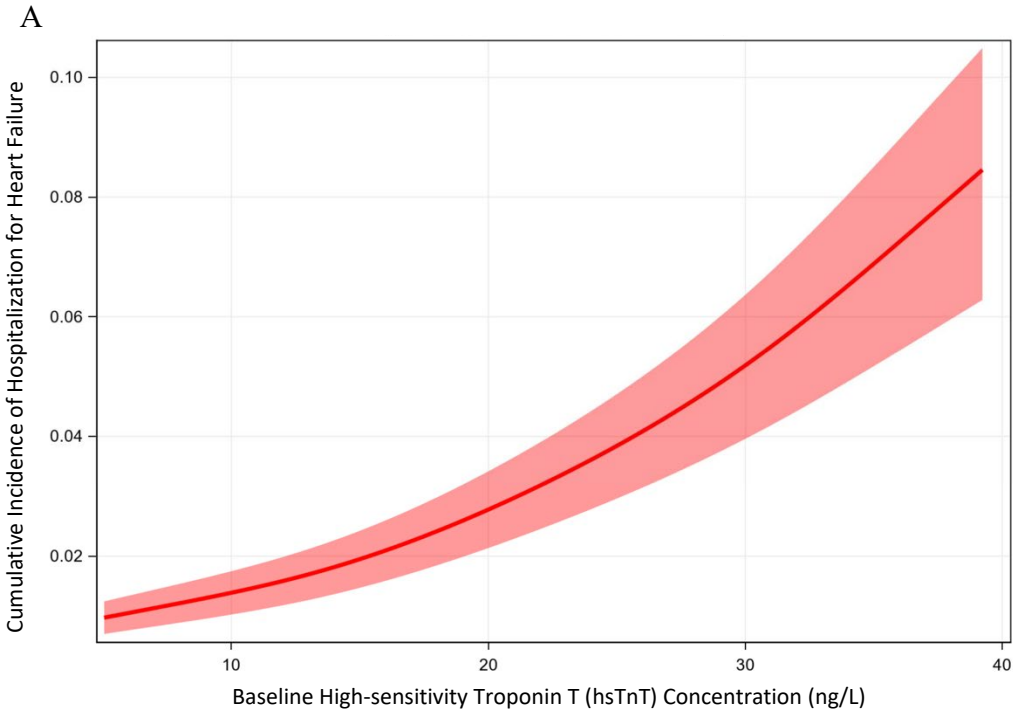
| | | | | | | | | | | |
|--|---------------|---------------|---------------|---------------|--------|---------------|---------------|---------------|---------------|--------|
| Prior myocardial infarction | 188 (14.2) | 409 (18.8) | 342 (21.7) | 620 (28.5) | <0.001 | 330 (12.7) | 451 (19.9) | 544 (31.0) | 234 (37.6) | <0.001 |
| Peripheral artery disease | 71 (5.4) | 104 (4.8) | 78 (5.0) | 184 (8.5) | <0.001 | 107 (4.1) | 136 (6.0) | 137 (7.8) | 57 (9.1) | <0.001 |
| Ischemic stroke | 80 (6.1) | 107 (4.9) | 111 (7.1) | 178 (8.2) | <0.001 | 150 (5.8) | 125 (5.5) | 136 (7.7) | 65 (10.4) | <0.001 |
| Prior heart failure | 62 (4.7) | 146 (6.7) | 158 (10.0) | 368 (16.9) | <0.001 | 86 (3.3) | 158 (7.0) | 267 (15.2) | 223 (35.8) | <0.001 |
| Atrial fibrillation | 27 (2.0) | 89 (4.1) | 124 (7.9) | 242 (11.1) | <0.001 | 44 (1.7) | 66 (2.9) | 157 (8.9) | 215 (34.5) | <0.001 |
| Percutaneous coronary intervention | 203 (15.4) | 440 (20.2) | 368 (23.4) | 582 (26.7) | <0.001 | 419 (16.1) | 481 (21.2) | 510 (29.0) | 183 (29.4) | <0.001 |
| Coronary artery bypass grafting | 52 (3.9) | 155 (7.1) | 169 (10.7) | 350 (16.1) | <0.001 | 101 (3.9) | 193 (8.5) | 291 (16.6) | 141 (22.6) | <0.001 |
| Dyslipidemia | 1041 (78.8) | 1734 (79.5) | 1300 (82.6) | 1810 (83.1) | <0.001 | 2125 (81.7) | 1799 (79.3) | 1437 (81.8) | 524 (84.1) | 0.019 |
| Hypertension | 1120 (84.8) | 1922 (88.2) | 1424 (90.5) | 2000 (91.9) | <0.001 | 2231 (85.8) | 2045 (90.1) | 1615 (91.9) | 575 (92.3) | <0.001 |
| Current smoker | 171 (12.9) | 312 (14.3) | 221 (14.0) | 299 (13.7) | 0.712 | 359 (13.8) | 323 (14.2) | 245 (13.9) | 76 (12.2) | 0.634 |
| | | | | | | | | | | |
| <i>Vital Signs</i> | | | | | | | | | | |
| Heart rate, median (25 th -75 th), bpm | 74 (68-80) | 72 (66-79) | 72 (65-80) | 72 (65-80) | <0.001 | 75 (68-82) | 72 (66-79) | 70 (64-77) | 72 (65-80) | <0.001 |
| Systolic blood pressure, median (25 th -75 th), mmHg | 132 (121-143) | 135 (125-145) | 135 (124-147) | 136 (125-147) | <0.001 | 133 (123-142) | 136 (125-146) | 138 (125-149) | 136 (125-147) | <0.001 |
| Diastolic blood pressure, median (25 th -75 th), mmHg | 79 (72-85) | 79 (72-85) | 79 (72-85) | 78 (71-84) | <0.001 | 79 (73-85) | 79 (72-84) | 78 (70-83) | 79 (71-85) | <0.001 |

Supplemental Figure 1. Relative strength of each variable in the multivariable risk model for hospitalization for heart failure. The relative contributions of each variable were assessed based on partial Wald χ^2 values. ACR, albumin/creatinine ratio; CAD, coronary artery disease; GFR, glomerular filtration rate; hsTnT, high-sensitivity troponin T; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

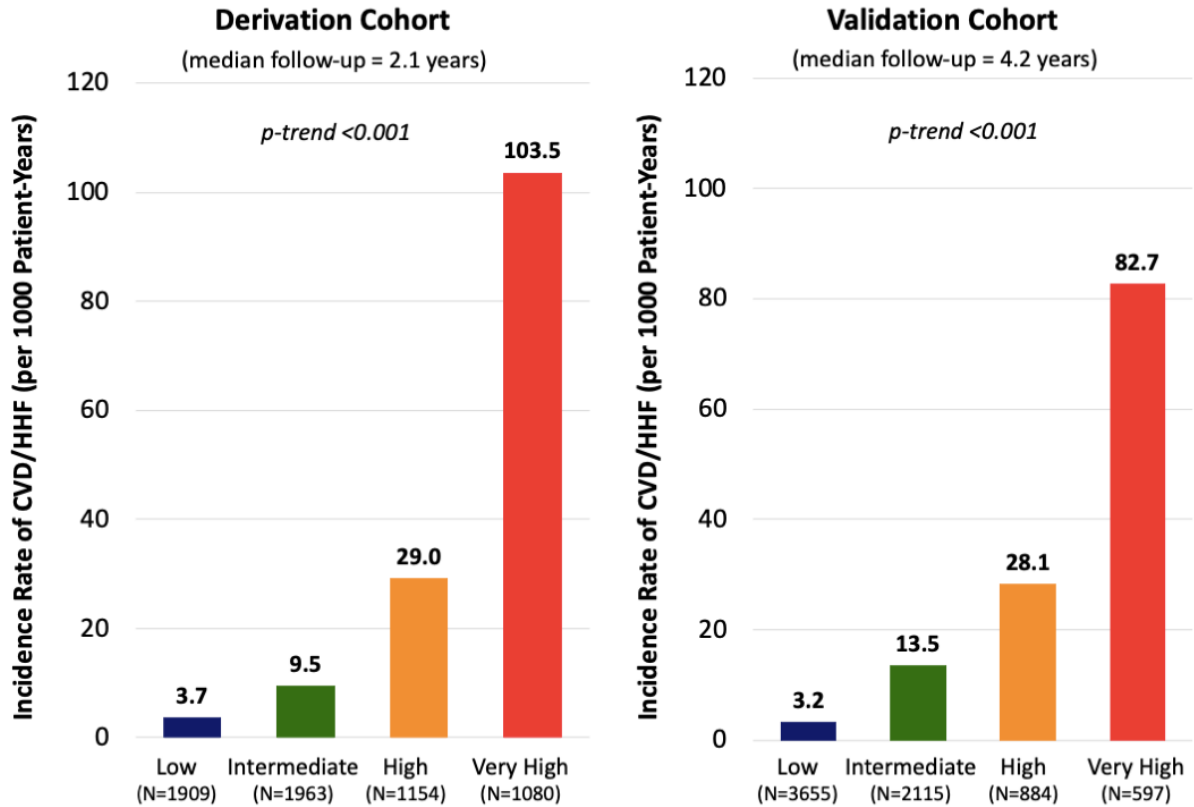


Supplemental Figure 2. Multivariable splines showing continuous relationships between baseline concentrations of (A) high-sensitivity troponin T (hsTnT) and (B) N-terminal pro-B type natriuretic peptide (NT-proBNP) and risk of hospitalization for heart failure (HHF).

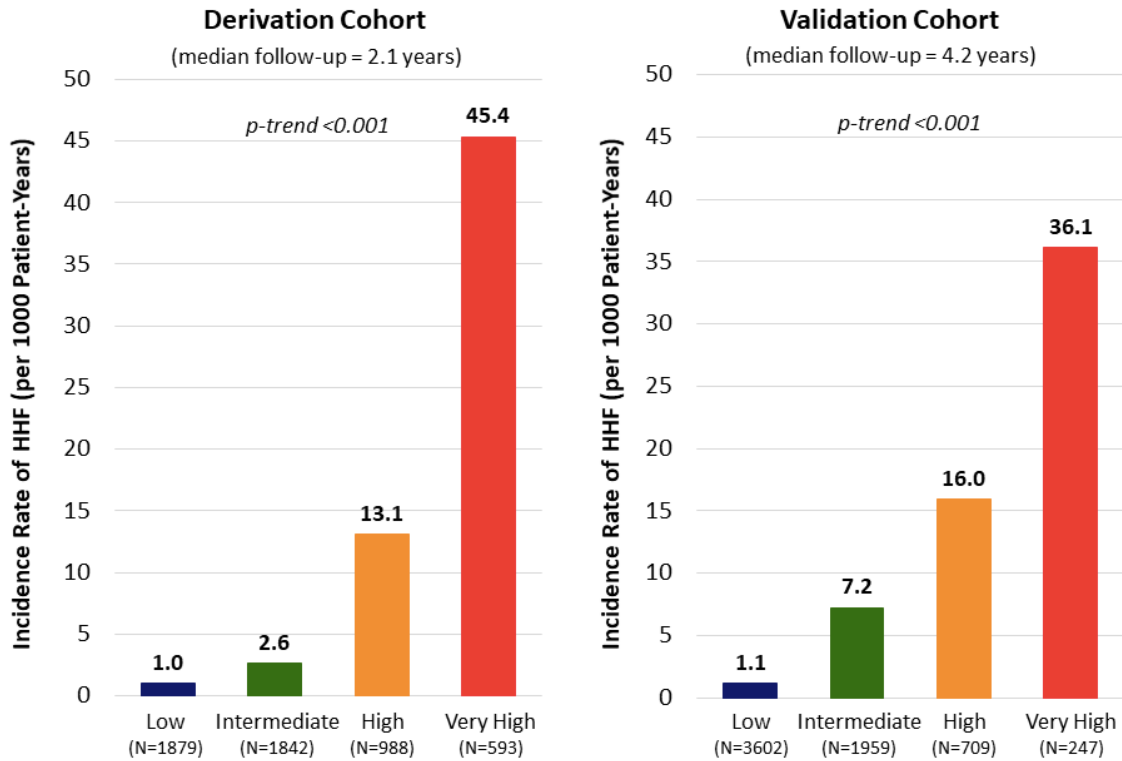
Graphed splines are truncated at the 5%ile-95%ile and are adjusted for the other biomarker of interest and history of heart failure



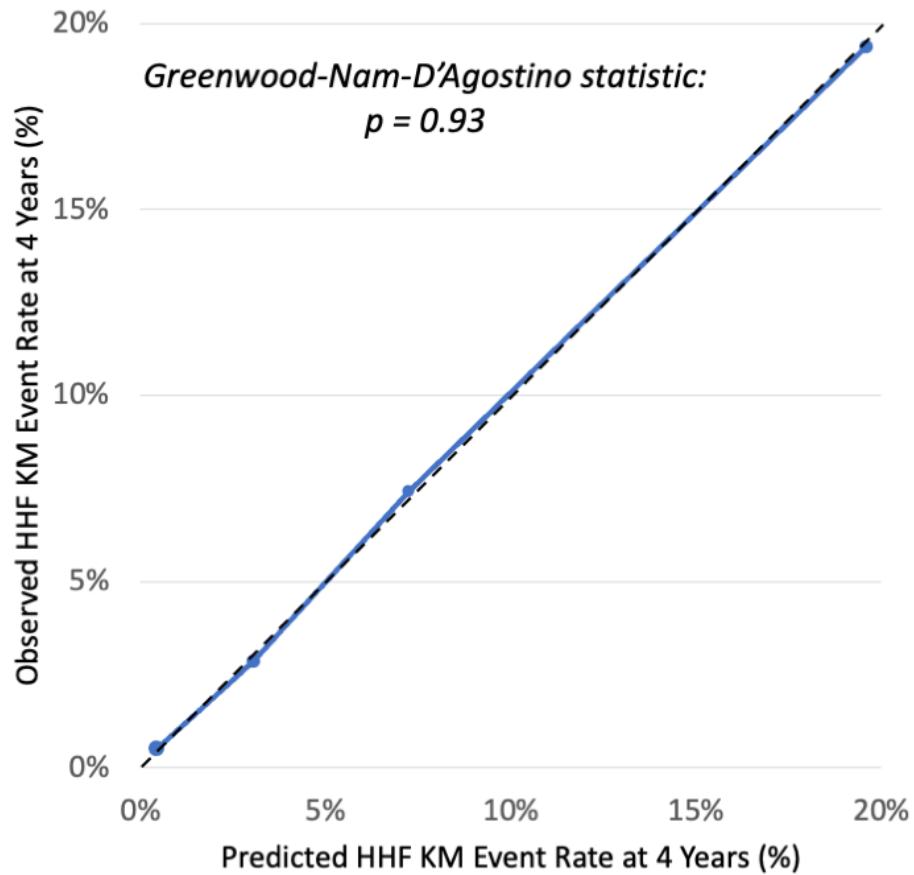
Supplemental Figure 3. Incidence rates of cardiovascular death or hospitalization for heart failure by risk category in the derivation and validation cohorts. The biomarker-based risk score identified significant gradients of risk for the composite endpoint of cardiovascular death or hospitalization for heart failure in the derivation and validation cohorts with comparable incidence rates in each cohort. The score had excellent discrimination for the composite endpoint, with c-indices of 0.82 and 0.81 in the derivation and validation cohorts, respectively. CVD, cardiovascular death; HHF, hospitalization for heart failure.



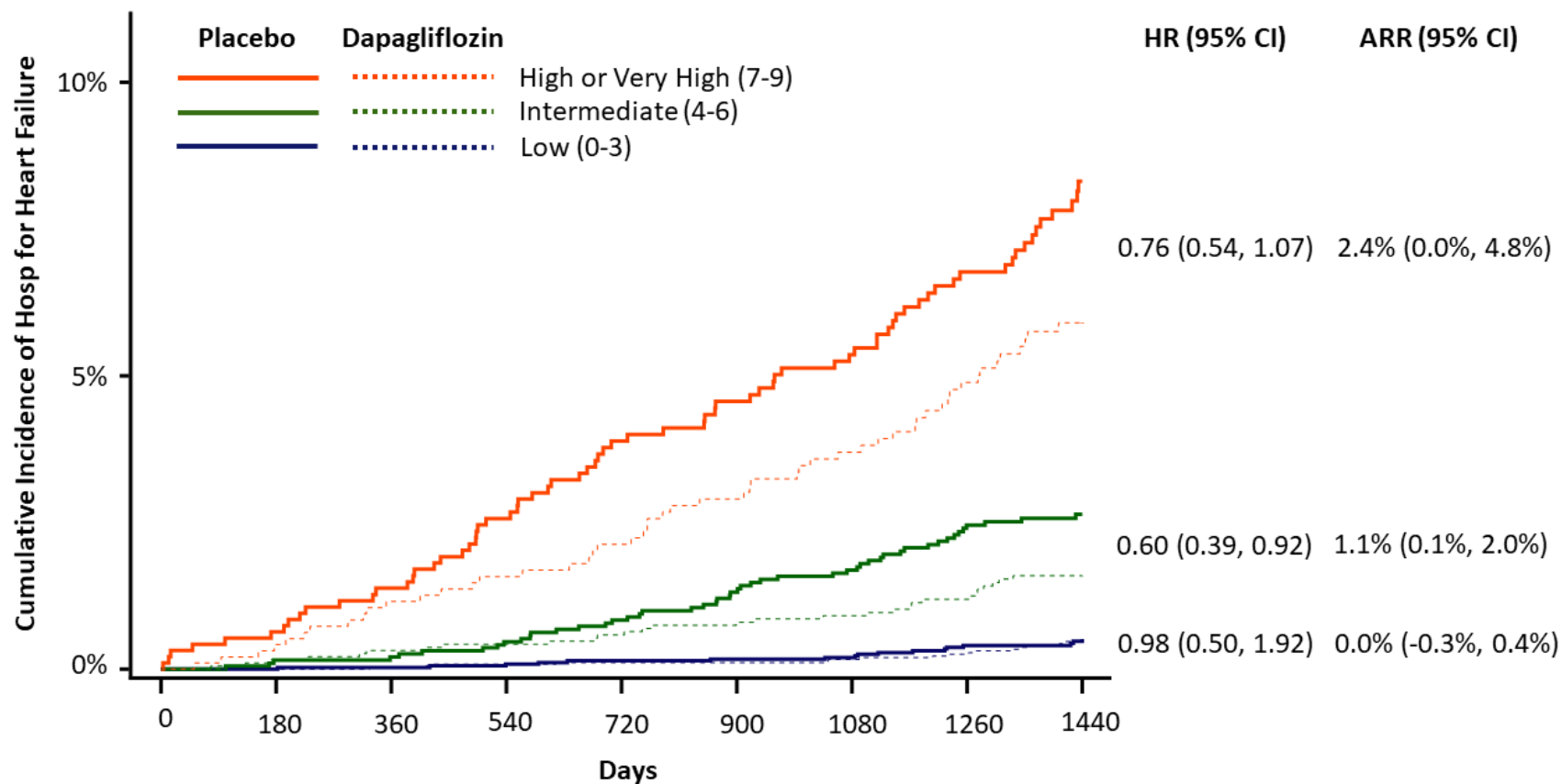
Supplemental Figure 4. Incidence rates of hospitalization for heart failure by risk category in the derivation and validation cohorts in patients without prior heart failure. Risk was categorized as low-risk (0-3 points), intermediate-risk (4-6 points), high-risk (7-8 points), and very high-risk (9 points). Note that the maximum score in patients without prior heart failure is only 9 points.



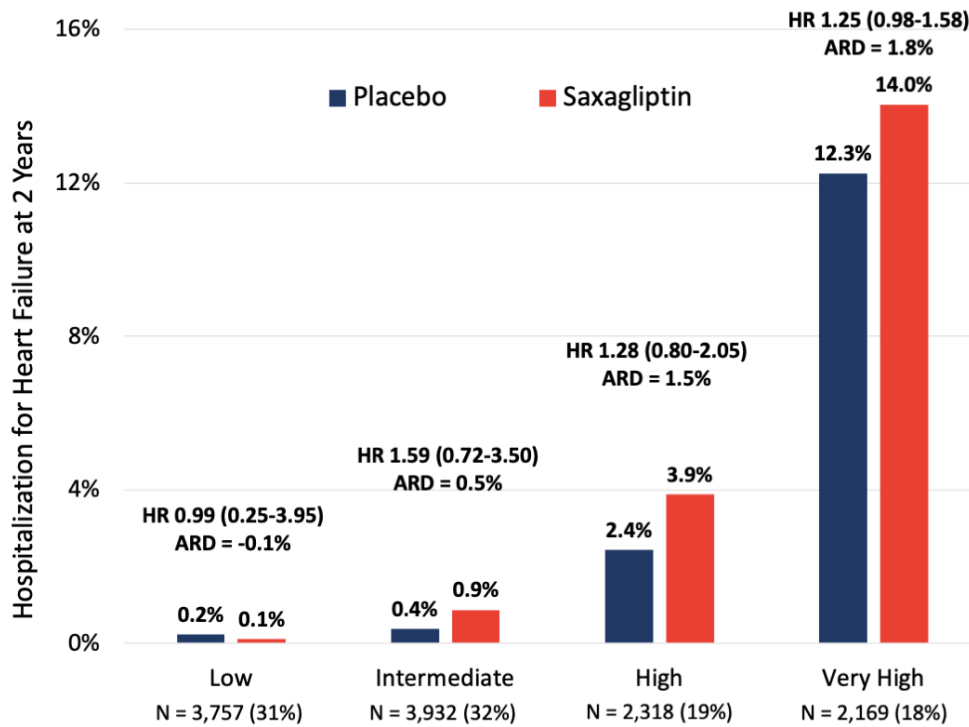
Supplemental Figure 5. Calibration plot of observed versus predicted rates of hospitalization for heart failure in the external validation cohort. The score had near-perfect calibration in the external validation cohort with a Greenwood-Nam-D'Agostino statistic of $p=0.93$ (non-significant p-values indicate adequate calibration). HHF, hospitalization for heart failure; KM, Kaplan-Meier.



Supplemental Figure 6. Treatment effect of dapagliflozin by risk category predicted by the biomarker-based risk score in patients without prior heart failure. Absolute risk reduction (ARR) was calculated by subtracting the Kaplan-Meier event rates for HHF at 4 years in patients treated with dapagliflozin from the Kaplan-Meier event rates for HHF at 4 years in patients treated with placebo across each risk score category. Note that the maximum score in patients without prior heart failure is only 9 points; therefore, the high- (7-8) and very high-risk (9-11) groups were collapsed in this figure. ARR, absolute risk reduction; HR, hazard ratio.



Supplemental Figure 7. Treatment effect of saxagliptin by risk category predicted by the biomarker-based risk score.



In the SAVOR-TIMI 53 trial, saxagliptin treatment was associated with an increased risk of hospitalization for heart failure (Scirica BM et al. *Circulation*. 2014 Oct 28;130(18):1579-88). We explored the relative and absolute risk differences in Kaplan-Meier (KM) event rates for HHF at 2 years with saxagliptin vs. placebo by risk category predicted by the biomarker-based risk score. Hazard ratios for HHF are shown for saxagliptin vs. placebo, and absolute risk differences (ARDs) are calculated based on differences in 2-year KM rates for HHF (saxagliptin – placebo). Patients in the low-risk group had a very low HHF event rate, and there was no difference between patients treated with saxagliptin vs. placebo. Among patients in the intermediate-, high-, and very high-risk categories, there was a higher risk of HHF in patients treated with saxagliptin vs. placebo (HR 1.26, 95% CI 1.03-1.55), with a gradient of absolute risk increase according to risk category predicted by the biomarker-based risk score (p-trend for ARD 0.003). ARD = absolute risk difference; CI = confidence interval; HR = hazard ratio; saxa = saxagliptin.