

Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Model Calibration and Creation of Risk Scores

Model Calibration

The final Cox model was first validated for Somers' Dxy rank correlation between predicted log hazard, observed survival time, and for slope shrinkage (Tables below). Bootstrapping was used (with 200 samples) to penalize for possible overfitting. Herein, "training" refers to the accuracy on the bootstrap sample used to fit the model, and "test" refers to the accuracy when this model is applied to the sample not used to fit the model. Using Table 1a as an example, the first column denotes the original index, which was -0.641. The column "Optimism" denotes the amount of overfitting by a model. The column "Corrected Index" is the original estimate minus the optimism. In this case, the bias-corrected Dxy is comparable to the original. The bias-corrected c-index (AUC) is $c = \frac{1 + |Dxy|}{2} = 0.82$, which performs well at predicting outcome.

Model validation results (Female)

	Original Sample	Training Sample	Test Sample	Optimism	Corrected Index
Dxy	-0.641	-0.647	0.636	-0.011	-0.630

Model validation results (Male)

	Original Sample	Training Sample	Test Sample	Optimism	Corrected Index
Dxy	-0.632	-0.633	-0.628	-0.004	-0.628

Creating risk scores from beta-coefficients in Cox model

A built in function in the statistical R package, `nomogram()`, was used to construct the nomogram. Manual calculation of building the nomogram using estimated beta coefficients from the Cox model is shown below.

Assigning risk points using Beta coefficients (Women)

Predictor	Level	Beta	Absolute maximum beta value	Rank	Assigned points
METs	≤5	3.4173	3.4173	1	10 assigned to MAXMETs≤5
	5-7	2.6633	2.6633	2	$10 \times (2.6633/3.4173) = 8$
	7-10	1.4452	1.4452	4	$10 \times (1.4452/3.4173) = 4$
	≥10				0
Abnormal HRR	1	0.6734	0.6734	7	$10 \times (0.6734/3.4173) = 2$
	0				0
Weight	<50 kg	1.4323	1.4323	5	$10 \times (1.4323/3.4173) = 4$
	50-70 kg	0.8718	0.8718	6	$10 \times (0.8718/3.4173) = 3$
	70-90 kg	0.5651	0.5651	9	$10 \times (0.5651/3.4173) = 2$
	≥90				0
ESRD	1	1.6696	1.6696	3	$10 \times (1.6696/3.4173) = 5$
	0				0
Age	>65	0.3430	0.3430	11	$10 \times (0.3430/3.4173) = 1$
	≤65				0
Former or current smoker	1	0.6296	0.6296	8	$10 \times (0.6296/3.4173) = 2$
	0				0
Diabetes	1	0.3858	0.3858	10	$10 \times (0.3858/3.4173) = 1$
	0				0

Assigning risk points using Beta coefficients (Men)

Predictor	Level	Beta	Absolute maximum beta value	Rank	Assigned points
METs	≤8	1.8835	1.8835	1	10 assigned to MAXMETs≤8
	8-10	1.0383	1.0383	4	$10 \times (1.0383/1.8835) = 6$
	10-12	0.7163	0.7163	7	$10 \times (0.7163/1.8835) = 4$
	≥12				0
Abnormal HRR	1	0.5863	0.5863	8	$10 \times (0.5863/1.8835) = 3$
	0				0
Weight	≤80 kg	0.2503	0.2503	11	$10 \times (0.2503/1.8835) = 1$
	>80 kg				0
ESRD	1	1.3453	1.3453	2	$10 \times (1.3453/1.8835) = 7$
	0				0
Age	≤55				0
	55-65	0.2437	0.2437	12	$10 \times (0.2437/1.8835) = 1$
	65-75	0.7186	0.7186	6	$10 \times (0.7186/1.8835) = 4$
	>75	1.2597	1.2597	3	$10 \times (1.2597/1.8835) = 7$
Former or current smoker	1	0.2777	0.2777	10	$10 \times (0.2777/1.8835) = 1$
Hypertension	1	0.3284	0.3284	9	$10 \times (0.3284/1.8835) = 2$
Heart Failure	1	1.0033	1.0033	5	$10 \times (1.0033/1.8835) = 5$

ESRD = End-stage renal disease; HRR = Heart rate recovery; METs = peak estimated metabolic equivalents

eTable 1. Baseline Clinical and Exercise Data for the FIT Cohort

Expressed as median (interquartile range) or n(%).

	Total (N=49,278)	Women (N=23,386)	Men (N=25,892)	<i>p</i> Value
Clinical Data				
Age	54.4 (46.4-64.1)	54.5 (46.7-64.3)	54.3 (46.0-64.0)	0.001
White	31,512 (64%)	13,967 (60%)	17,545 (68%)	
BMI	28.7 (25.4-32.8)	28.9 (25.1-33.7)	28.5 (25.7-31.9)	<0.001
History of HTN	33,554 (68%)	16,028 (69%)	17,526 (68%)	0.044
History of DM	10,703 (21%)	5,001 (21%)	5,702 (22%)	0.086
History of Dyslipidemia	23,673 (48%)	10,795 (46%)	12,878 (50%)	<0.001
History of CHF	1,122 (2%)	470 (2%)	652 (3%)	0.001
GFR<15	234 (<1%)	101 (<1%)	133 (<1%)	0.187
Exercise Data				
Resting SBP, mmHg	130 (118-142)	130 (116-142)	130 (120-142)	<0.001
Resting heart rate, BPM	72 (64-81)	73 (66-82)	70 (62-79)	<0.001
Peak SBP, mmHg	178 (160-196)	172 (156-190)	180 (162-200)	<0.001
Peak heart rate, BPM	150 (135-162)	150 (136-161)	150 (134-163)	0.345
%MPHR Achieved	90.6 (85.0-96.1)	90.7 (85.4-96.2)	90.6 (84.5-96.1)	0.001
METS Achieved	10 (7-10)	7 (7-10)	10 (7-13)	<0.001

BMI = body mass index, BP = blood pressure, CHF = congestive heart failure, GFR = glomerular filtration rate, METs

= estimated metabolic equivalents

eTable 2. Univariable Associations With All-Cause Mortality

Expressed as median (interquartile range) or n (%).

	Women (n=24,292)			Men (n=35,585)		
	Survived (n=23,550)	Death (n=742)	<i>P</i>	Survived (n=33,806)	Death (n=1,779)	<i>P</i>
Clinical Data						
Age (years)	53(45-62)	65(55-74)	<.001	53(45-62)	66(55.5-74)	<.001
BMI (kg/m ²)	27.5(23.7-32.3)	27(23.5-31.6)	.07	28.2(25.6-31.4)	28(25-31.3)	.003
Body Weight (kg)	73(63-86)	70(61-82)	<.001	90(80-101)	88(77-99)	<.001
Diabetes	2,468 (13)	167 (34)	<.001	3,850 (16)	439 (37)	<.001
Hypertension	10,113 (44)	497 (68)	<.001	15,328 (46)	1,204 (68)	<.001
Hyperlipidemia	11,178 (49)	432 (59)	<.001	18,927 (57)	1,057 (60)	.005
H/O smoking	9,328 (40)	407 (55)	<.001	15,978 (48)	1,181 (67)	<.001
Current smoker	2,858 (12)	130 (18)	<.001	4,070 (12)	303 (17)	<.001
Family H/O CAD	8,389 (36)	266 (37)	.73	10,751 (32)	521 (30)	.04
CAD	2,039 (9)	186 (25)	<.001	7,863 (23)	767 (43)	<.001
Previous MI	881 (4)	76 (10)	<.001	3,459 (10)	350 (20)	<.001
Previous PCI	771 (3)	82 (11)	<.001	3,212 (10)	305 (17)	<.001
Previous CABG	410 (2)	56 (8)	<.001	2,385 (7)	330 (19)	<.001
COPD	295 (2)	54 (9)	<.001	438 (2)	113 (7)	<.001
Stroke/TIA	484 (3)	48 (8)	<.001	708 (3)	110 (7)	<.001
CHF	291 (2)	42 (7)	<.001	454 (2)	131 (9)	<.001
ESRD	65 (0)	19 (3)	<.001	141 (1)	39 (3)	<.001
PVD	194 (1)	27 (4)	<.001	376 (1)	87 (6)	<.001

Medications						
Aspirin	6,927 (29)	301 (41)	<.001	14,515 (43)	949 (53)	<.001
Clopidogrel	803 (3)	53 (7)	<.001	2,309 (7)	174 (10)	<.001
Beta Blocker	5,413 (23)	270 (36)	<.001	8,447 (25)	718 (40)	<.001
ACEI/ARB	4,839 (21)	271 (37)	<.001	9,118 (27)	736 (41)	<.001
Statin	5,697 (27)	253 (36)	<.001	12,265 (42)	775 (46)	.001
Exercise Data						
Rest HR	73(65-81)	76(67-86)	<.001	67(60-76)	69(61-80)	<.001
Rest systolic BP	126(112-140)	136(120-150)	<.001	130(118-140)	134(122-150)	<.001
Rest RPP	9.2(7.8-10.8)	10.2(8.6-12.2)	<.001	8.7(7.4-10.2)	9.2(7.9-11.2)	<.001
No ST depression	19,062 (81)	566 (76)	.002	26,505 (78)	1,311 (74)	<.001
Chest pain	532 (3)	20 (5)	.04	984 (6)	87 (11)	<.001
Termination due to chest pain	347 (1)	15 (2)	.29	517 (2)	48 (3)	<.001
Maximum HR	157(145-171)	139(125-153)	<.001	160(144-171)	139(123-151)	<.001
Maximum RPP	26.9(23.4-30.4)	24.2(19.8-28.2)	<.001	29.2(25.3-32.9)	24.5(20.2-29)	<.001
Delta RPP	17.4(14-20.7)	13.4(9.5-17.5)	<.001	20.3(16.3-23.9)	14.7(10.4-19.1)	<.001
Peak METs	8(6.8-10)	6(5.0-7.0)	<.001	10(8.5-11.6)	7(6.0-8.9)	<.001
Abnormal HRR	3,615 (15)	333 (45)	<.001	4,942 (15)	814 (46)	<.001
Abnormal CRI	4,684 (20)	309 (42)	<.001	5,493 (16)	670 (38)	<.001
DTS	6.5(4.5-8.5)	4.5(2.5-5.5)	<.001	8.5(5.5-10.3)	5.5(2.5-7.3)	<.001

ACE = angiotension converting enzyme inhibitor; ARB = angiotension receptor blocker; BP= blood pressure; CABG = coronary artery bypass surgery; CAD=coronary artery disease; CCF = Cleveland Clinic Foundation; CHF= congestive heart failure; COPD= chronic obstructive lung disease; CP = chest pain; CRI = chronotropic response index; DTS = Duke Treadmill Score; Delta RPP = Maximal RPP – resting RPP; ESRD= end-stage renal disease; H/O = history of; HRR = heart rate recovery; METs = estimated metabolic equivalents; MI= myocardial infarction; PCI=percutaneous coronary intervention; PVD = peripheral vascular disease; RPP = rate-pressure product; TIA = transient ischemic attack.

eTable 3. Multivariable Cox Proportional Hazards Models for Prediction of Mortality in Females and Males

	Female		Male	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Peak METs	0.67(0.63-0.72)	<.001	0.73(0.70-0.76)	<.001
Abnormal HRR	1.86(1.48-2.34)	<.001	1.60(1.37-1.86)	<.001
Age (yr)	1.02(1.01-1.03)	<.001	1.03(1.02-1.04)	<.001
Weight (kg)	0.98(0.98-0.99)	<.001	0.99(0.99-1)	<.001
ESRD	4.23(1.71-10.42)	.002	4.33(2.72-6.9)	<.001
Former or current smoking	1.95(1.58-2.42)	<.001	1.20(1.04-1.39)	.01
Diabetes	1.45(1.14-1.86)	.003		
Heart Failure			2.26(1.77-2.9)	<.001
Hypertension			1.32(1.12-1.55)	<.001

CHF = congestive heart failure; ESRD = end stage renal disease; H/O = history of; HRR = heart rate recovery; METs = estimated metabolic equivalents

eTable 4. Estimated 10-Year Mortality for Women in the CCF Cohort (n = 24 292) According to Sex-Specific Risk Scores

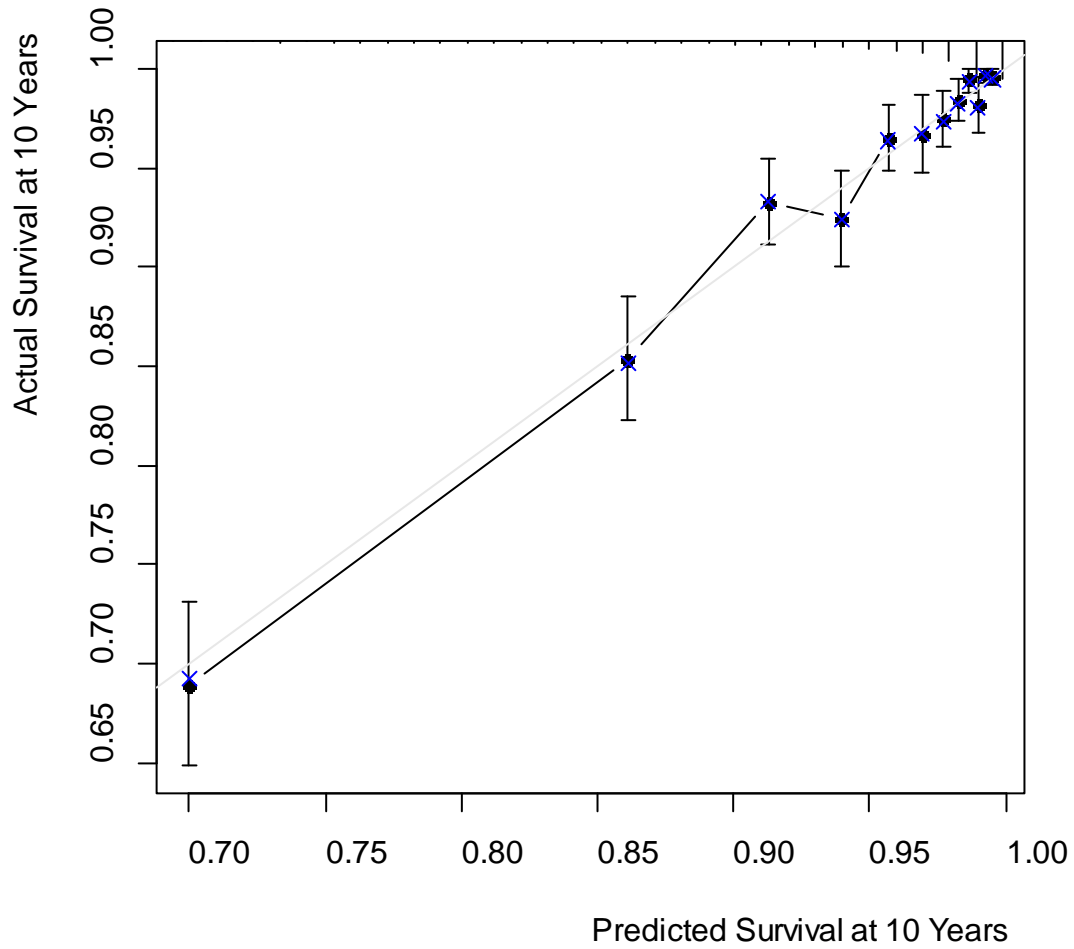
Risk score	Risk of 10 year mortality	95%	CI
0	0.001	0.001	0.001
1	0.002	0.001	0.002
2	0.002	0.002	0.003
3	0.003	0.002	0.004
4	0.004	0.003	0.005
5	0.006	0.005	0.007
6	0.008	0.007	0.009
7	0.011	0.01	0.013
8	0.016	0.014	0.017
9	0.021	0.019	0.023
10	0.03	0.027	0.032
11	0.04	0.038	0.043
12	0.055	0.051	0.058
13	0.073	0.069	0.078
14	0.097	0.091	0.103
15	0.126	0.118	0.134
16	0.16	0.149	0.171
17	0.199	0.184	0.212
18	0.24	0.223	0.256
19	0.282	0.262	0.3
20	0.322	0.302	0.341
21	0.358	0.338	0.377
22	0.39	0.371	0.407
23	0.416	0.399	0.431
24	0.437	0.423	0.45
25	0.453	0.442	0.464

CCF = Cleveland Clinic Foundation, CI = Confidence Interval

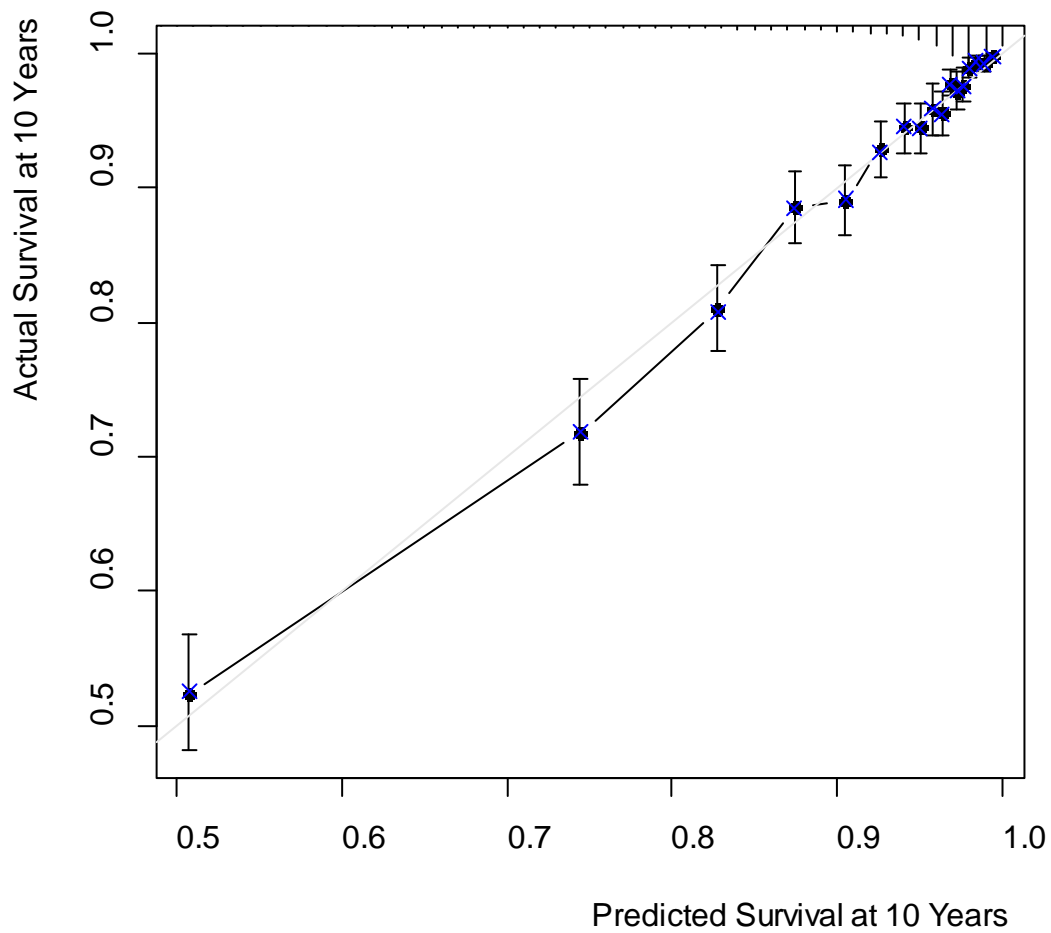
eTable 5. Estimated 10-Year Mortality for Men in the CCF Cohort (n = 35 585) According to Sex-Specific**Risk Scores**

Risk score	Risk of 10 year mortality	95%	CI
0	0.006	0.005	0.006
1	0.007	0.006	0.008
2	0.009	0.008	0.009
3	0.01	0.009	0.011
4	0.013	0.011	0.014
5	0.015	0.014	0.017
6	0.019	0.017	0.02
7	0.023	0.021	0.025
8	0.028	0.026	0.03
9	0.034	0.032	0.036
10	0.041	0.038	0.043
11	0.049	0.047	0.051
12	0.059	0.056	0.061
13	0.07	0.067	0.073
14	0.083	0.08	0.087
15	0.099	0.095	0.102
16	0.116	0.111	0.12
17	0.135	0.13	0.14
18	0.156	0.15	0.162
19	0.178	0.172	0.185
20	0.202	0.195	0.21
21	0.227	0.219	0.236
22	0.253	0.243	0.262
23	0.278	0.268	0.288
24	0.303	0.292	0.314
25	0.327	0.316	0.338
26	0.349	0.338	0.36
27	0.37	0.359	0.38
28	0.388	0.378	0.398
29	0.405	0.395	0.415
30	0.42	0.411	0.429
31	0.433	0.424	0.441
32	0.444	0.436	0.451
33	0.453	0.446	0.46
34	0.461	0.455	0.467
35	0.468	0.462	0.473
36	0.473	0.469	0.478

eFigure 1. Predicted Survival at 10 Years in Men and Women in the Derivation Cohort

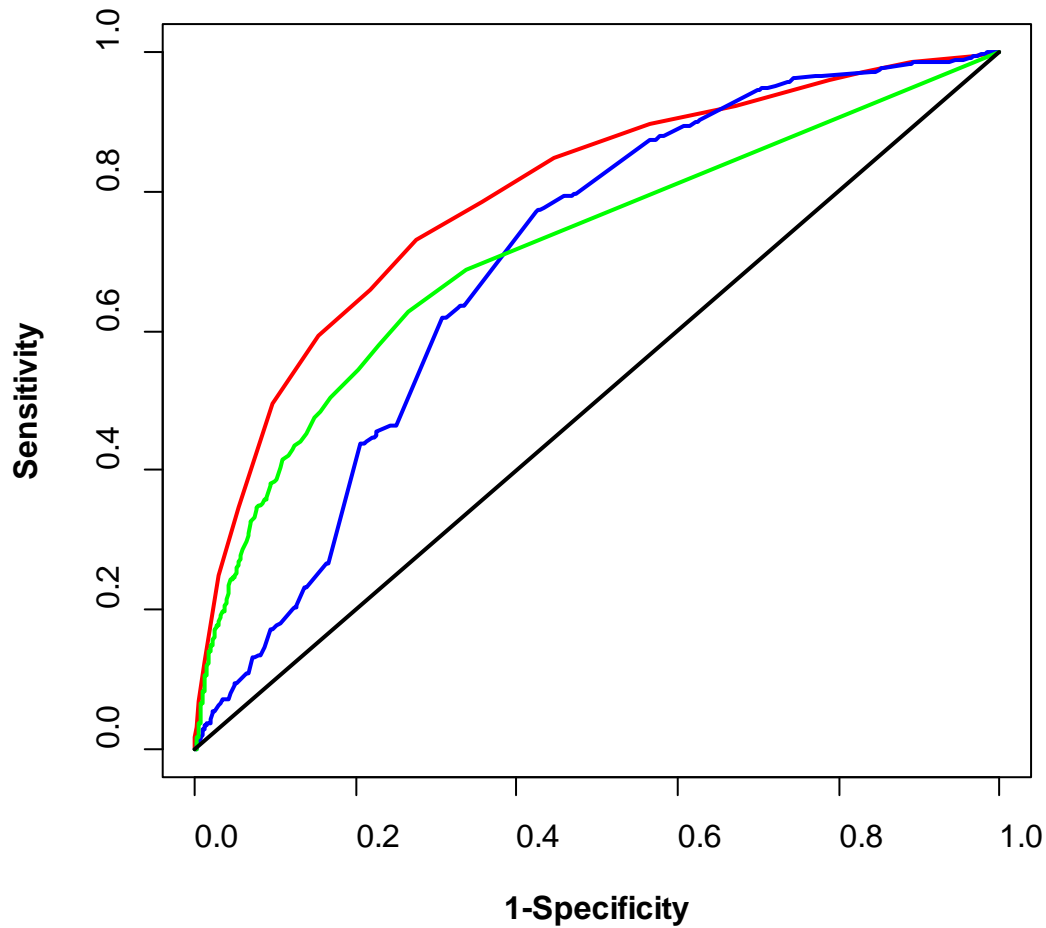


eFigure 1A. Bootstrap estimates of calibration accuracy for the final Cox models in women (derivation cohort, $n = 12,152$). Dots correspond to predictive accuracy, and Xs mark bootstrap corrected estimated. The plotted curve (solid line) tracks well with the ideal curve (dashed line).



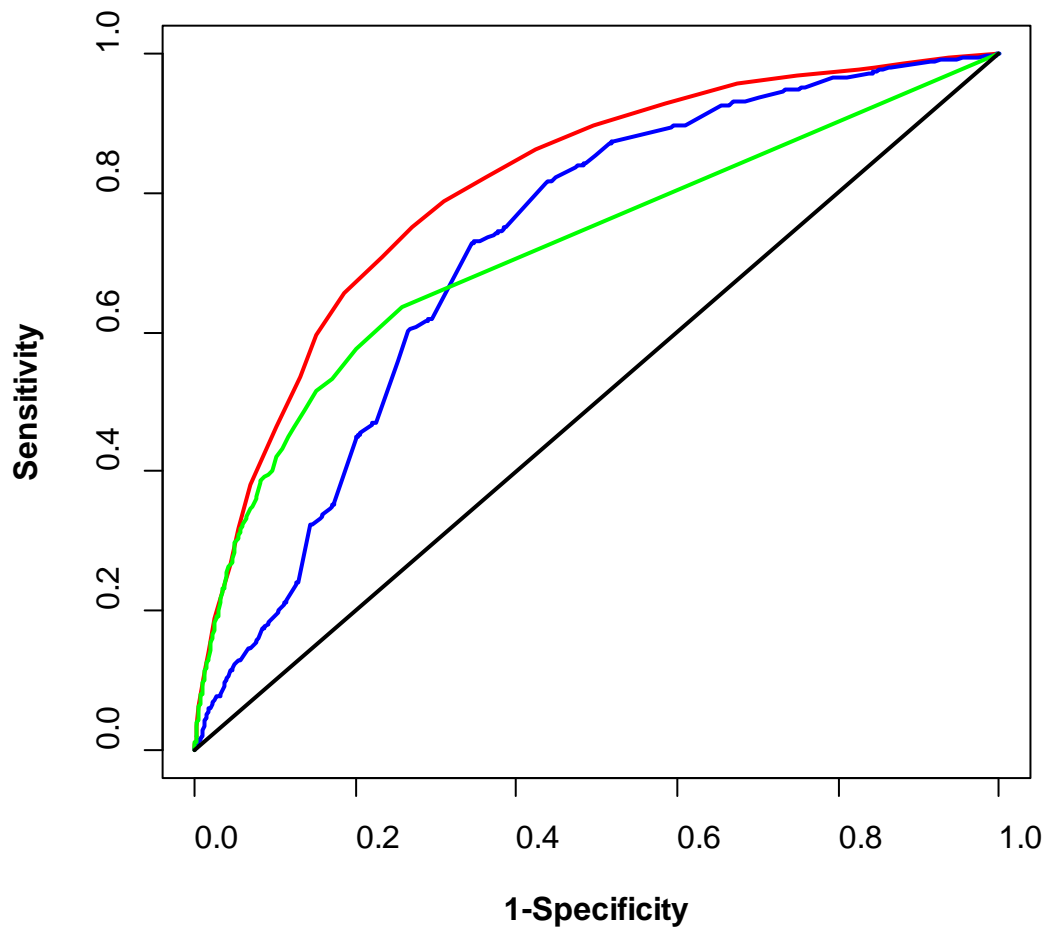
eFigure 1B. Bootstrap estimates of calibration accuracy for the final Cox models in men (derivation cohort, n = 17,892). Dots correspond to predictive accuracy, and Xs mark bootstrap corrected estimated. The plotted curve (solid line) tracks well with the ideal curve (dashed line).

eFigure 2. ROC Curves in Men and Women in the CCF Validation Cohort



eFigure 2A. ROC curves comparing the new sex-specific risk score to the DTS and Lauer nomogram in women in the CCF validation cohort (n = 12,140). The sex-specific NRS is shown in red (C-statistic 0.79), the Lauer nomogram in green (C-statistic 0.74), and the DTS in blue (C-statistic 0.70).

CCF = Cleveland Clinic Foundation, DTS = Duke Treadmill Score, NRS = Sex-specific new risk score, ROC = Receiver operating characteristic



eFigure 2B. ROC curves comparing the sex-specific risk score to the DTS and Lauer nomogram in men in the CCF validation cohort (n = 17,693). The sex-specific new risk score is shown in red (C-statistic 0.81), the Lauer nomogram in green (C-statistic 0.75), and the DTS in blue (C-statistic 0.72).

CCF = Cleveland Clinic Foundation, DTS = Duke Treadmill Score, NRS = Sex-specific new risk score, ROC = Receiver operating characteristic