

## Supplemental Material

## Supplemental Methods

### Comparison of hematology-based survival model with pooled-cohort equations for ASCVD risk.

*Endpoints: acute coronary syndrome or stroke or death*

To approximate the outcome modeled by the pooled-cohort equations, we created a composite outcome from these three single-event outcomes: 1) fatal or nonfatal AI-adjudicated acute coronary syndrome (ACS); 2) fatal or nonfatal AI-adjudicated ischemic stroke (IS); 3) death. We determine that a patient has this composite outcome, “ACS/IS/death”, as soon as they have one or more of these three single-event outcomes.

#### *Model training*

To approximate the model-derivation cohort used for the pooled-cohort equations, we selected the subset of our model-derivation cohort that met the following two criteria: 1) patient’s age is between 40 and 79 years; 2) patient had no AI-adjudicated events before they entered our study, i.e., no ACS, no HF, no IS, no PCI/CABG. This left us with 15844 patients. To build a corresponding validation cohort, we applied the same two criteria to the validation cohort from the main study, but also excluded anyone who did not have a 3-year PCE risk score (see below).

We trained Cox proportional-hazards models for the composite outcome ASC/IS/death in the same way we trained models for all other outcomes in this study. We examined only the age-hematology predictor set (AGE-HEM).

#### *Model evaluation*

We evaluated model predictions at 3 years. We measured discrimination using the cumulative/dynamic area under the ROC curve (CDAUC)<sup>53</sup>. We used the implementation of CDAUC in the Python package scikit-survival v0.14.0. Values reported are point estimates of CDAUC using survival at 3 years, not the average CDAUC over 3 years. We measure Brier score at 3 years, as described earlier in the main Methods section.

We evaluated each model only on the people for whom we could calculate PCE risk. Our validation cohort consisted of 10964 people. Our derivation cohort consisted of 15844 people, but the testing stage of *k*-fold cross validation was performed only on the 6524 of them who had 3-year PCE risk scores.

#### *Model comparison*

We compared the hematology-based model to the 3-year PCE risk model using the same methods that we used to compare two different sets of predictors. The only modification is that we used CDAUC instead of the C-index. A difference in CDAUC or Brier score between the two models is presented as a mean and 95% CI, obtained by bootstrapping (for validation cohort) or by repeated K-fold cross validation (for derivation cohort).

## Supplemental Figures and Figure Legends

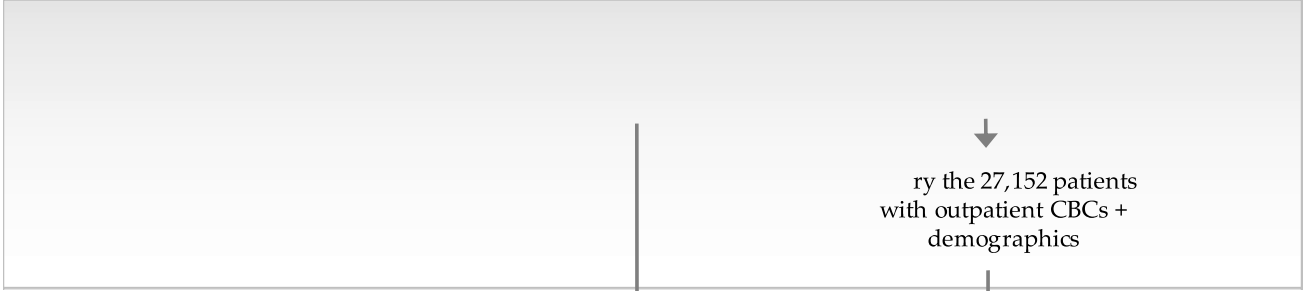
Electronic Data Warehouse



Query the 31,397 patients  
with outpatient CBCs

**Supplemental Figure 1A: Flow diagram for patient inclusion and exclusion for modeling CVD events in derivation cohort**

MGH patients and their data, used to model time-to-event for all outcomes except death.



ry the 27,152 patients  
with outpatient CBCs +  
demographics



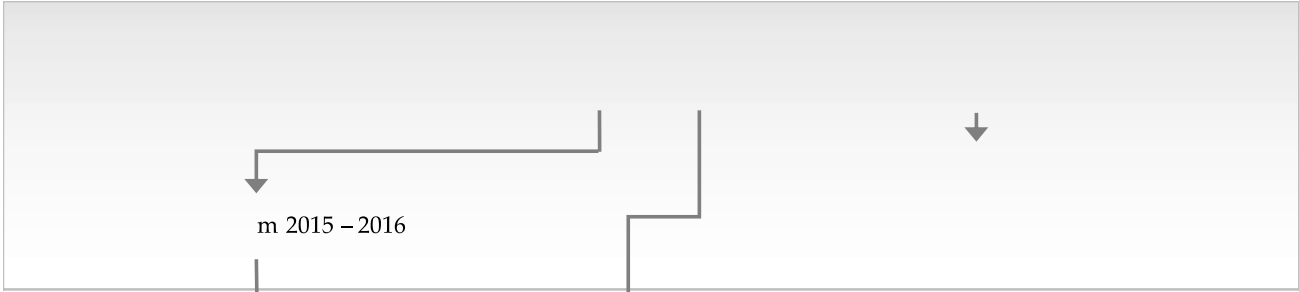
**Supplemental Figure 1B: Flow diagram for modeling death in derivation cohort**  
MGH patients and their data, used to model time-to-event for death



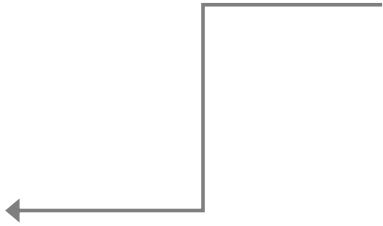


**Supplemental Figure 1C: Flow diagram for patient inclusion and exclusion for modeling CVD events in validation cohort**

BWH patients and their data, used to model time-to-event for all outcomes except death.



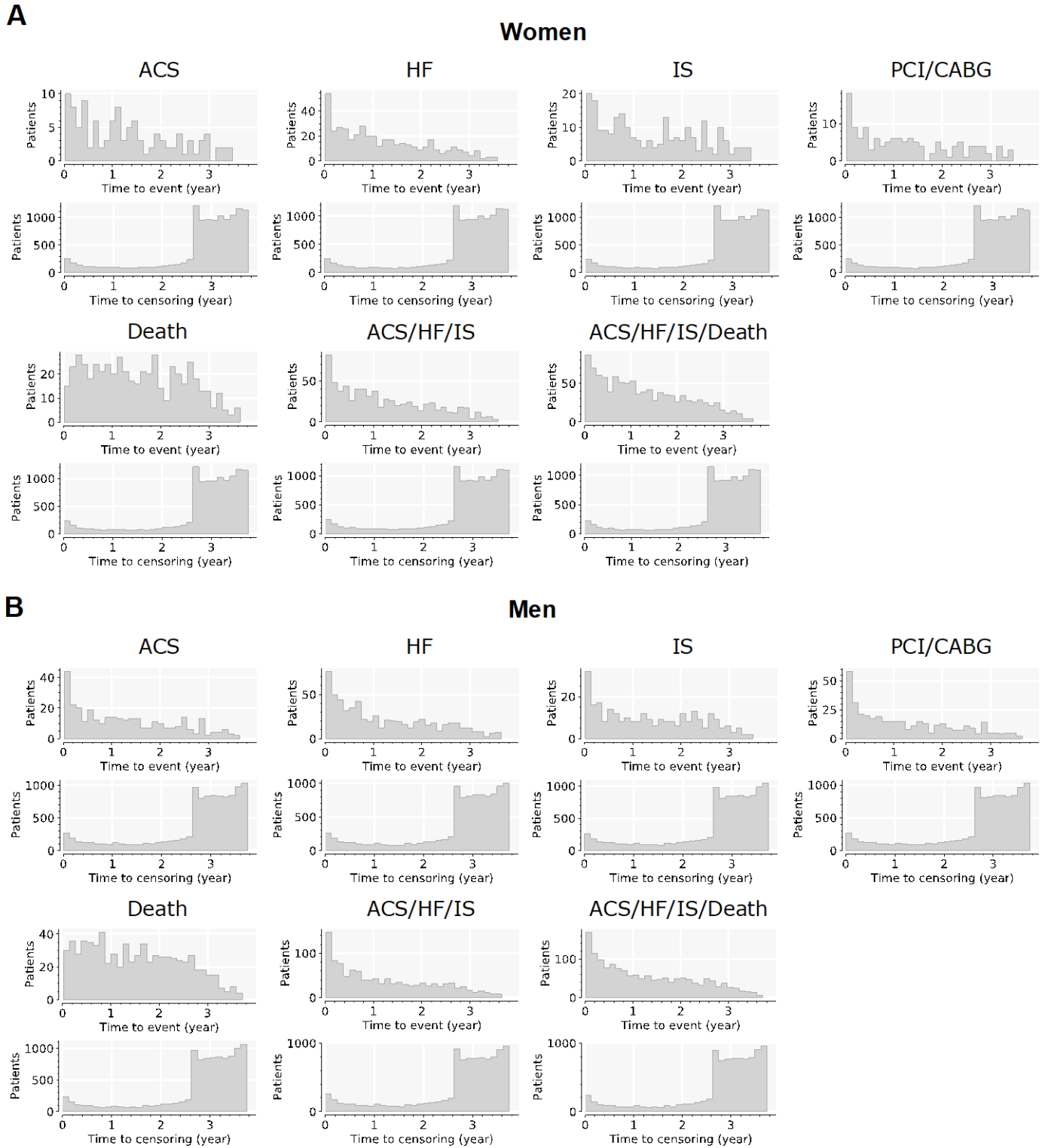
- 654,843 CBCs
- 141,743 patients



**Supplemental Figure 1D: Flow diagram for modeling death in validation cohort**

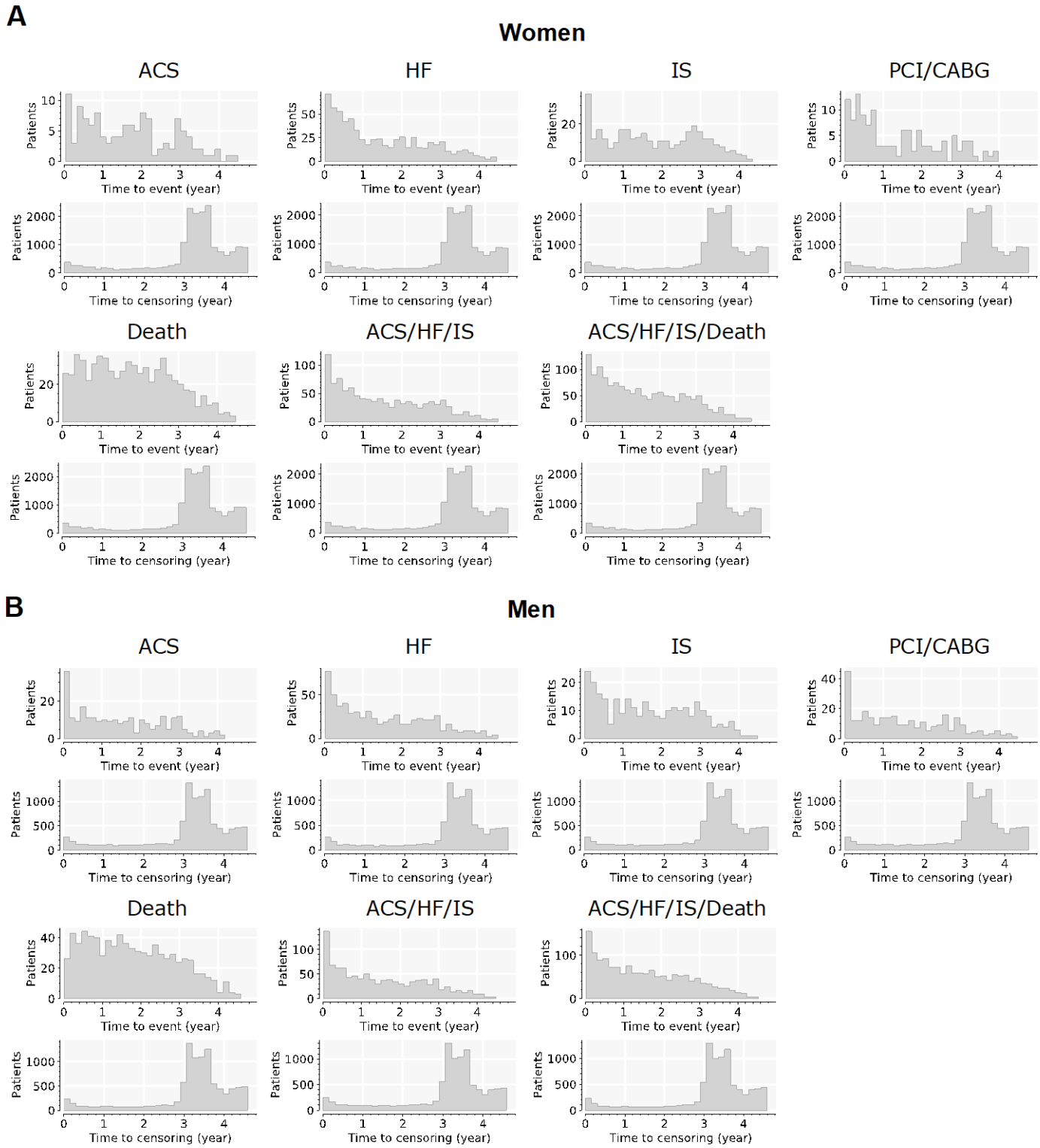
BWH patients and their data, used to model time-to-event for death

**Supplemental Figure 2. Distribution of time to events in derivation cohort.**



**Supplemental Figure 2:** Time to first outcome (or to right-censoring, for patients without outcomes in the observation period). Results broken down by the seven outcomes for women (**A**) and men (**B**) in this study. Derivation cohort. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke; PCI/CABG = percutaneous coronary intervention / coronary artery bypass graft

### Supplemental Figure 3. Distribution of time to events in validation cohort.



**Supplemental Figure 3:** Time to first outcome (or to right-censoring, for patients without outcomes in the observation period). Results broken down by the seven outcomes for women (**A**) and men (**B**) in this study. Validation cohort. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke; PCI/CABG = percutaneous coronary intervention / coronary artery bypass graft



## Supplemental Tables

**Supplemental Table 1. Glossary of medical terms**

Term	Definition
Encounter	Any interaction of a patient with a medical system, including laboratory draws, imaging tests, outpatient visits, and hospital admissions.
Discharge summary	A detailed description of the clinical course for a hospitalization encounter
Lab-order identifier	Unique value assigned to each laboratory order
Note	A written account describing details of a medical encounter.
Problem list	Enumeration of current active medical problems for a patient.
Diagnostic code	Alphanumerical codes assigned to descriptions of diseases, illnesses and injuries.
Encounter diagnosis	Diagnostic code assigned to an encounter, usually to facilitate reimbursement from payers.
Structured data	Medical information captured in tables and usually reflecting selections from a finite number of elements (e.g., diagnostic codes). Contrasted with “unstructured” data, which includes sentences found in medical notes.

**Supplemental Table 2. Performance of artificial-intelligence models for CVD-event adjudication.**

Event	Sensitivity	Specificity	Precision
ACS	0.76	0.97	0.59
HF	0.94	0.91	0.58
IS	0.80	0.97	0.64
PCI/CABG	0.98	0.99	0.90

**Supplemental Table 2:** Performance of classifier algorithms used to adjudicate outcomes for our study. Classification thresholds were chosen to maximize  $F_1$  score. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke; PCI/CABG = percutaneous coronary intervention / coronary artery bypass graft

**Supplemental Table 3. Performance of ICD10 codes in predicting history of disease**

Past History	Sensitivity	Specificity
ACS	0.78	0.95
HF	0.68	0.95
IS	0.95	0.93

**Supplemental Table 3:** ICD10 codes can predict a patient’s history of disease at the time of their entry into the survival study. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke

**Supplemental Table 4. Main effects, notation, and description**

Predictor Symbol	Description of predictor	Transformation parameters			
		Women		Men	
		Mean	Std. Dev.	Mean	Std. Dev.
HCT	Hematocrit. Volume fraction of whole blood which is red cells (%)	39.4	3.83	42.0	4.79
HGB	Hemoglobin concentration. Concentration of hemoglobin in whole blood, in units of mass per volume (g/dL)	12.9	1.42	14.0	18.0
MCH	Mean corpuscular hemoglobin. Average hemoglobin content per red cell, in units of mass (pg)	29.5	2.50	30.1	2.32
MCHC	Mean corpuscular hemoglobin concentration. Average hemoglobin concentration inside red cells, in units of mass per volume (g/dL)	32.7	1.22	33.3	1.32
MCV	Mean corpuscular volume. The average volume of a single red cell (fL)	90.1	6.35	90.4	5.90
MPV	Mean platelet volume. The average volume of a single platelet (fL)	10.4	1.65	10.5	1.59
PLT	Platelet count. The number of platelets per volume of whole blood ( $10^9$ cells / L)	262	79.0	219	70.9
RBC	Red blood cell count. The number of red cells per volume of whole blood ( $10^{12}$ cells / L)	4.39	0.477	4.67	0.599
RDW	Red cell volume distribution width (C.V.). Standard deviation of red cell volume, divided by mean corpuscular volume (%)	13.9	1.64	13.8	1.55
WBC	White blood cell count. The number of white cells per volume of whole blood ( $10^9$ cells / L)	6.98	3.34	7.14	3.86
age	Patient's age at time of entry into survival study (years)	57.4	15.0	60.1	14.3
Hx_CAD	History of coronary disease or heart attack before entry into study	-	-	-	-
Hx_HF	History of heart failure before entry into study	-	-	-	-
Hx_stroke	History of stroke before entry into study	-	-	-	-

**Supplemental Table 4:** Main effects of the proportional-hazards models referred to in this study. All main effects are unitless in the proportional-hazards model. Except for the three history predictors, all predictors in this table must be transformed by subtracting their mean and then dividing by their standard deviation, as measured in the derivation cohort. Means and standard deviations used for this transformation are shown in the four rightmost columns. Units for these values are in the 2<sup>nd</sup> column from left. The history variables are binary (0 for no history; 1 for yes history of disease) and are not scaled or centered. Transformation parameters are shown for datasets that don't include death as an outcome. To get the transformation parameters for the ACS/HF/IS/death model and death models, apply these five substitutions: (MCV, women std): 63.5 → 63.6; (RBC, men mean): 467 → 466; (HCT, men std): 47.9 → 48.0; (PLT, men std): 70.9 → 71.0; (RBC, men std): 59.9 → 60.1.

**Supplemental Table 5. Terms used in the five predictor sets for survival models**

Predictor Set	Terms in predictor set
hematology-only	HCT, HGB, MCH, MCHC, MCV, MPV, PLT, RBC, RDW, WBC
age-hematology	HCT, HGB, MCH, MCHC, MCV, MPV, PLT, RBC, RDW, WBC, age, HCT x age, HGB x age, MCHC x age, MCH x age, MCV x age, MPV x age, PLT x age, RBC x age, RDW x age, WBC x age, age x age
age-hematology-history	HCT, HGB, MCH, MCHC, MCV, MPV, PLT, RBC, RDW, WBC, age, Hx_CAD, Hx_HF, Hx_stroke, HCT x age, HGB x age, MCHC x age, MCH x age, MCV x age, MPV x age, PLT x age, RBC x age, RDW x age, WBC x age, age x age, Hx_CAD x age, Hx_HF x age, Hx_stroke x age
age-history	age, Hx_CAD, Hx_HF, Hx_stroke, age x age, Hx_CAD x age, Hx_HF x age, Hx_stroke x age
age-only	age, age x age,

**Supplemental Table 5:** The elements in each list are the terms,  $X_i$ , in the linear predictor of the Cox proportional-hazards model. An explanation of notation is in Supplemental Table 4 “Main effects, notation, and description”

**Supplemental Table 6. Model performance, according to Brier score at 3 years**

Pred. Set	Outcome	Brier Score, Internal Test Set		Brier Score, External Validation Set	
		Women	Men	Women	Men
HEM	ACS	0.006 (0.005 to 0.007)	0.023 (0.020 to 0.026)	0.010 (0.010 to 0.010)	0.031 (0.031 to 0.031)
	HF	0.032 (0.029 to 0.034)	0.051 (0.047 to 0.054)	0.036 (0.036 to 0.036)	0.054 (0.054 to 0.055)
	IS	0.016 (0.015 to 0.018)	0.024 (0.021 to 0.027)	0.020 (0.020 to 0.020)	0.028 (0.028 to 0.028)
	PCI/CABG	0.006 (0.005 to 0.008)	0.026 (0.023 to 0.029)	0.012 (0.012 to 0.012)	0.036 (0.036 to 0.036)
	death	0.031 (0.029 to 0.033)	0.057 (0.053 to 0.061)	0.042 (0.041 to 0.043)	0.057 (0.057 to 0.058)
	ACS/HF/IS	0.048 (0.045 to 0.051)	0.080 (0.075 to 0.084)	0.057 (0.057 to 0.057)	0.091 (0.091 to 0.091)
	ACS/HF/IS/death	0.065 (0.062 to 0.068)	0.104 (0.099 to 0.108)	0.077 (0.076 to 0.078)	0.113 (0.113 to 0.113)
AGE HEM	ACS	0.006 (0.005 to 0.007)	0.023 (0.020 to 0.026)	0.010 (0.010 to 0.010)	0.031 (0.031 to 0.031)
	HF	0.031 (0.028 to 0.033)	0.051 (0.047 to 0.055)	0.034 (0.034 to 0.035)	0.054 (0.054 to 0.054)
	IS	0.016 (0.014 to 0.018)	0.024 (0.021 to 0.027)	0.020 (0.020 to 0.020)	0.027 (0.027 to 0.027)
	PCI/CABG	0.007 (0.005 to 0.008)	0.026 (0.023 to 0.029)	0.012 (0.012 to 0.012)	0.036 (0.036 to 0.036)
	death	0.031 (0.029 to 0.033)	0.055 (0.052 to 0.059)	0.040 (0.039 to 0.041)	0.056 (0.055 to 0.056)
	ACS/HF/IS	0.046 (0.043 to 0.049)	0.079 (0.075 to 0.083)	0.054 (0.054 to 0.054)	0.090 (0.089 to 0.090)
	ACS/HF/IS/death	0.061 (0.058 to 0.063)	0.100 (0.096 to 0.104)	0.072 (0.071 to 0.073)	0.110 (0.110 to 0.111)
AGE HEM HX	ACS	0.006 (0.005 to 0.007)	0.023 (0.020 to 0.025)	0.010 (0.010 to 0.010)	0.030 (0.030 to 0.030)
	HF	0.029 (0.026 to 0.031)	0.046 (0.043 to 0.050)	0.032 (0.032 to 0.032)	0.050 (0.049 to 0.050)
	IS	0.016 (0.014 to 0.018)	0.023 (0.021 to 0.026)	0.020 (0.020 to 0.020)	0.027 (0.027 to 0.027)
	PCI/CABG	0.006 (0.005 to 0.007)	0.026 (0.023 to 0.028)	0.011 (0.011 to 0.012)	0.035 (0.035 to 0.035)
	death	0.028 (0.026 to 0.031)	0.055 (0.051 to 0.059)	0.039 (0.039 to 0.040)	0.054 (0.054 to 0.055)
	ACS/HF/IS	0.044 (0.041 to 0.047)	0.073 (0.069 to 0.077)	0.051 (0.051 to 0.051)	0.084 (0.084 to 0.085)
	ACS/HF/IS/death	0.059 (0.056 to 0.062)	0.097 (0.093 to 0.101)	0.068 (0.068 to 0.068)	0.106 (0.106 to 0.106)
AGE HX	ACS	0.006 (0.005 to 0.007)	0.023 (0.020 to 0.025)	0.010 (0.010 to 0.010)	0.030 (0.030 to 0.030)
	HF	0.029 (0.027 to 0.032)	0.048 (0.044 to 0.051)	0.033 (0.033 to 0.033)	0.051 (0.051 to 0.051)
	IS	0.016 (0.014 to 0.018)	0.023 (0.021 to 0.026)	0.020 (0.020 to 0.020)	0.027 (0.027 to 0.027)
	PCI/CABG	0.006 (0.005 to 0.007)	0.025 (0.023 to 0.028)	0.011 (0.011 to 0.011)	0.035 (0.035 to 0.035)
	death	0.030 (0.028 to 0.032)	0.059 (0.055 to 0.062)	0.041 (0.040 to 0.041)	0.059 (0.059 to 0.059)
	ACS/HF/IS	0.044 (0.042 to 0.047)	0.076 (0.072 to 0.079)	0.052 (0.052 to 0.053)	0.087 (0.086 to 0.087)
	ACS/HF/IS/death	0.061 (0.058 to 0.064)	0.102 (0.098 to 0.107)	0.072 (0.072 to 0.072)	0.112 (0.112 to 0.112)
AGE	ACS	0.006 (0.005 to 0.007)	0.023 (0.020 to 0.026)	0.010 (0.010 to 0.010)	0.031 (0.031 to 0.031)
	HF	0.032 (0.030 to 0.035)	0.055 (0.051 to 0.059)	0.037 (0.037 to 0.037)	0.058 (0.058 to 0.058)
	IS	0.016 (0.015 to 0.018)	0.024 (0.021 to 0.027)	0.020 (0.020 to 0.020)	0.028 (0.028 to 0.028)
	PCI/CABG	0.006 (0.005 to 0.008)	0.026 (0.023 to 0.029)	0.012 (0.012 to 0.012)	0.036 (0.036 to 0.036)
	death	0.032 (0.030 to 0.035)	0.062 (0.058 to 0.067)	0.044 (0.044 to 0.044)	0.064 (0.064 to 0.064)
	ACS/HF/IS	0.049 (0.046 to 0.052)	0.086 (0.081 to 0.090)	0.060 (0.060 to 0.060)	0.097 (0.097 to 0.097)
	ACS/HF/IS/death	0.068 (0.065 to 0.071)	0.116 (0.112 to 0.121)	0.083 (0.083 to 0.083)	0.126 (0.126 to 0.126)

**Supplemental Table 6:** Mean and 95% confidence intervals for Brier score at 3 years. For 7 outcomes modeled with 5 predictor sets (HEM = hematology-only , AGE-HEM = age-hematology, HEM-HX = hematology-history, AGE-HX = age-history, and AGE = age-only). The distribution of C-index on the derivation dataset is obtained by repeated *k*-fold cross-validation. The distribution on the validation dataset is obtained by bootstrapping inputs to a final model trained on the entire derivation dataset. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke; PCI/CABG = percutaneous coronary intervention / coronary artery bypass graft

**Supplemental Table 7. Model performance, according to C-index**

Pred. Set	Outcome	C-Index, Internal Test Set		C-Index, External Validation Set	
		Women	Men	Women	Men
AGE HEM	ACS	0.730 (0.691 to 0.747)	0.648 (0.631 to 0.662)	0.764 (0.728 to 0.799)	0.659 (0.629 to 0.688)
	HF	0.790 (0.778 to 0.794)	0.787 (0.782 to 0.790)	0.730 (0.706 to 0.753)	0.811 (0.795 to 0.827)
	IS	0.768 (0.760 to 0.774)	0.696 (0.685 to 0.702)	0.737 (0.712 to 0.763)	0.734 (0.704 to 0.762)
	PCI/CABG	0.732 (0.708 to 0.747)	0.682 (0.675 to 0.687)	0.753 (0.711 to 0.792)	0.675 (0.647 to 0.702)
	death	0.826 (0.818 to 0.832)	0.817 (0.816 to 0.818)	0.842 (0.826 to 0.856)	0.803 (0.788 to 0.818)
	ACS/HF/IS	0.779 (0.777 to 0.780)	0.727 (0.724 to 0.728)	0.718 (0.700 to 0.736)	0.755 (0.741 to 0.770)
	ACS/HF/IS/death	0.790 (0.783 to 0.794)	0.752 (0.751 to 0.753)	0.760 (0.747 to 0.774)	0.769 (0.757 to 0.780)
HEM HX	ACS	0.763 (0.750 to 0.777)	0.742 (0.731 to 0.754)	0.753 (0.698 to 0.804)	0.725 (0.689 to 0.757)
	HF	0.805 (0.801 to 0.808)	0.838 (0.835 to 0.839)	0.773 (0.751 to 0.795)	0.847 (0.833 to 0.861)
	IS	0.744 (0.738 to 0.750)	0.696 (0.687 to 0.702)	0.673 (0.642 to 0.704)	0.703 (0.669 to 0.735)
	PCI/CABG	0.758 (0.745 to 0.767)	0.755 (0.747 to 0.760)	0.746 (0.690 to 0.796)	0.718 (0.687 to 0.747)
	death	0.798 (0.794 to 0.800)	0.807 (0.806 to 0.808)	0.787 (0.768 to 0.806)	0.791 (0.775 to 0.806)
	ACS/HF/IS	0.782 (0.779 to 0.783)	0.770 (0.769 to 0.771)	0.737 (0.719 to 0.756)	0.780 (0.766 to 0.794)
	ACS/HF/IS/death	0.781 (0.780 to 0.782)	0.775 (0.774 to 0.776)	0.749 (0.735 to 0.763)	0.775 (0.764 to 0.786)
AGE HX	ACS	0.803 (0.796 to 0.807)	0.775 (0.770 to 0.780)	0.828 (0.790 to 0.864)	0.764 (0.733 to 0.792)
	HF	0.787 (0.784 to 0.789)	0.771 (0.769 to 0.773)	0.707 (0.680 to 0.734)	0.813 (0.795 to 0.829)
	IS	0.766 (0.759 to 0.770)	0.705 (0.701 to 0.709)	0.742 (0.716 to 0.769)	0.736 (0.709 to 0.762)
	PCI/CABG	0.804 (0.798 to 0.812)	0.771 (0.762 to 0.775)	0.816 (0.775 to 0.855)	0.767 (0.740 to 0.791)
	death	0.768 (0.767 to 0.769)	0.741 (0.740 to 0.742)	0.798 (0.782 to 0.814)	0.732 (0.714 to 0.749)
	ACS/HF/IS	0.780 (0.779 to 0.781)	0.746 (0.746 to 0.747)	0.724 (0.704 to 0.743)	0.773 (0.758 to 0.787)
	ACS/HF/IS/death	0.767 (0.766 to 0.767)	0.735 (0.735 to 0.736)	0.740 (0.726 to 0.753)	0.748 (0.735 to 0.760)
AGE	ACS	0.706 (0.679 to 0.726)	0.650 (0.642 to 0.655)	0.744 (0.707 to 0.779)	0.656 (0.623 to 0.687)
	HF	0.698 (0.686 to 0.716)	0.655 (0.651 to 0.657)	0.644 (0.619 to 0.670)	0.718 (0.697 to 0.739)
	IS	0.729 (0.722 to 0.732)	0.659 (0.648 to 0.671)	0.713 (0.687 to 0.739)	0.704 (0.674 to 0.732)
	PCI/CABG	0.706 (0.685 to 0.726)	0.658 (0.651 to 0.665)	0.723 (0.682 to 0.766)	0.670 (0.642 to 0.696)
	death	0.741 (0.728 to 0.746)	0.714 (0.704 to 0.716)	0.777 (0.759 to 0.793)	0.712 (0.694 to 0.729)
	ACS/HF/IS	0.719 (0.712 to 0.721)	0.656 (0.652 to 0.657)	0.670 (0.652 to 0.689)	0.700 (0.685 to 0.716)
	ACS/HF/IS/death	0.722 (0.722 to 0.722)	0.670 (0.667 to 0.670)	0.702 (0.688 to 0.716)	0.699 (0.686 to 0.712)

**Supplemental Table 7:** Mean and 95% confidence intervals for C-index. For 7 outcomes modeled with 4 predictor sets (AGE-HEM = age-hematology, HEM-HX = hematology-history, AGE-HX = age-history, and AGE = age-only). The distribution of C-index on the derivation dataset is obtained by repeated *k*-fold cross-validation. The distribution on the validation dataset is obtained by bootstrapping inputs to a final model trained on the entire derivation dataset. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke; PCI/CABG = percutaneous coronary intervention / coronary artery bypass graft

**Supplemental Table 8. Comparison of pairs of predictor sets according to C-index**

Pred. Set	Outcome	$\Delta_c$ , Derivation Dataset		$\Delta_c$ , Validation Dataset	
		Women	Men	Women	Men
A: AGE HX  B: AGE	ACS	0.097 (0.079 to 0.122) * †	0.126 (0.118 to 0.133) * †	0.084 (0.054 to 0.116) *	0.108 (0.077 to 0.141) *
	HF	0.089 (0.071 to 0.100) * †	0.116 (0.113 to 0.121) * †	0.062 (0.050 to 0.075) *	0.094 (0.077 to 0.112) *
	IS	0.038 (0.029 to 0.046) * †	0.046 (0.036 to 0.059) * †	0.030 (0.018 to 0.043) *	0.032 (0.017 to 0.050) *
	PCI/CABG	0.098 (0.077 to 0.118) * †	0.113 (0.100 to 0.121) * †	0.092 (0.062 to 0.125) *	0.097 (0.069 to 0.126) *
	death	0.027 (0.022 to 0.040) * †	0.026 (0.024 to 0.037) * †	0.021 (0.014 to 0.029) *	0.020 (0.012 to 0.029) *
	ACS/HF/IS	0.061 (0.059 to 0.067) * †	0.090 (0.089 to 0.094) * †	0.054 (0.044 to 0.063) *	0.073 (0.061 to 0.086) *
	ACS/HF/IS/death	0.045 (0.044 to 0.045) * †	0.066 (0.065 to 0.069) * †	0.038 (0.031 to 0.045) *	0.049 (0.040 to 0.058) *
A: AGE HEM HX  B: AGE HEM	ACS	0.079 (0.061 to 0.115) * †	0.121 (0.105 to 0.145) * †	0.075 (0.044 to 0.107) *	0.103 (0.074 to 0.134) *
	HF	0.034 (0.030 to 0.045) * †	0.052 (0.049 to 0.057) * †	0.026 (0.016 to 0.037) *	0.044 (0.034 to 0.054) *
	IS	0.018 (0.014 to 0.024) * †	0.026 (0.018 to 0.033) * †	0.011 (0.005 to 0.018) *	0.014 (0.002 to 0.027) *
	PCI/CABG	0.075 (0.061 to 0.095) * †	0.091 (0.084 to 0.097) * †	0.074 (0.047 to 0.105) *	0.088 (0.062 to 0.115) *
	death	0.007 (-0.005 to 0.019)	0.004 (0.003 to 0.005) *	0.007 (0.002 to 0.011) *	0.002 (-0.002 to 0.005)
	ACS/HF/IS	0.030 (0.028 to 0.031) * †	0.049 (0.046 to 0.051) * †	0.030 (0.022 to 0.038) *	0.038 (0.030 to 0.048) *
	ACS/HF/IS/death	0.022 (0.017 to 0.028) * †	0.030 (0.028 to 0.031) * †	0.019 (0.014 to 0.025) *	0.020 (0.014 to 0.025) *
A: AGE HEM  B: HEM	ACS	0.098 (0.066 to 0.129) * †	0.054 (0.033 to 0.075) * †	0.145 (0.097 to 0.193) *	0.063 (0.034 to 0.090) *
	HF	0.032 (0.020 to 0.040) *	0.004 (-0.001 to 0.009)	-0.002 (-0.018 to 0.015)	0.007 (0.003 to 0.012) *
	IS	0.066 (0.059 to 0.076) * †	0.043 (0.029 to 0.051) * †	0.101 (0.074 to 0.128) *	0.053 (0.029 to 0.074) *
	PCI/CABG	0.088 (0.063 to 0.119) * †	0.049 (0.042 to 0.056) * †	0.139 (0.095 to 0.189) *	0.066 (0.044 to 0.089) *
	death	0.046 (0.032 to 0.063) * †	0.022 (0.020 to 0.023) * †	0.080 (0.068 to 0.093) *	0.018 (0.010 to 0.026) *
	ACS/HF/IS	0.051 (0.048 to 0.059) * †	0.013 (0.011 to 0.015) * †	0.037 (0.022 to 0.052) *	0.026 (0.019 to 0.033) *
	ACS/HF/IS/death	0.049 (0.041 to 0.059) * †	0.017 (0.015 to 0.018) * †	0.052 (0.040 to 0.063) *	0.024 (0.018 to 0.031) *
A: HEM HX  B: HEM	ACS	0.131 (0.116 to 0.149) * †	0.147 (0.133 to 0.161) * †	0.134 (0.084 to 0.186) *	0.129 (0.093 to 0.165) *
	HF	0.048 (0.043 to 0.056) * †	0.055 (0.052 to 0.061) * †	0.041 (0.025 to 0.058) *	0.044 (0.034 to 0.055) *
	IS	0.042 (0.037 to 0.056) * †	0.044 (0.034 to 0.054) * †	0.037 (0.022 to 0.053) *	0.022 (0.009 to 0.036) *
	PCI/CABG	0.114 (0.100 to 0.140) * †	0.122 (0.114 to 0.128) * †	0.132 (0.087 to 0.183) *	0.109 (0.079 to 0.141) *
	death	0.018 (0.008 to 0.032) * †	0.011 (0.010 to 0.013) * †	0.025 (0.017 to 0.035) *	0.007 (0.002 to 0.012) *
	ACS/HF/IS	0.053 (0.050 to 0.061) * †	0.056 (0.055 to 0.057) * †	0.056 (0.046 to 0.068) *	0.051 (0.041 to 0.061) *
	ACS/HF/IS/death	0.040 (0.035 to 0.050) * †	0.040 (0.039 to 0.041) * †	0.040 (0.032 to 0.048) *	0.030 (0.023 to 0.038) *

**Supplemental Table 8:** Mean and 95% confidence interval of the statistic  $\Delta_c = C_A - C_B$ , where  $C_A$  is the C-index of an outcome modeled with predictor set A, and  $C_B$  is the C-index for an outcome modeled with predictor set B. Six predictor sets shown (AGE-HEM = age-hematology, AGE = age-only, AGE-HX = age-history, AGE-HEM-HX = age-hematology-history, HEM = hematology-only, HEM-HX = hematology-history). An asterisk ( \* ) denotes that  $\Delta_c$  is significantly different from zero. A cross ( † ) next to a derivation-set result denotes that that  $\Delta_c$  is also significantly different from zero in the validation set, and the effect is in the same direction as in the derivation dataset, i.e. the result in the derivation set is corroborated by the result in the validation set). There were no cases where a validation-set result was significant, but in the opposite direction of a significant derivation-set

result. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke; PCI/CABG = percutaneous coronary intervention / coronary artery bypass graft



**Supplemental Table 9. Comparison of pairs of predictor sets according to 3-year Brier Score**

Pred. Set	Outcome	$\Delta$ s, Derivation Dataset		$\Delta$ s, Validation Dataset	
		Women	Men	Women	Men
A: AGE HEM  B: AGE	ACS	6E-5 (-4E-5 to 2E-4)	2E-5 (-5E-5 to 1E-4)	-4E-5 (-5E-5 to -2E-5) *	5E-6 (-7E-5 to 8E-5)
	HF	-3E-3 (-3E-3 to -2E-3) * †	-4E-3 (-4E-3 to -4E-3) * †	-1E-3 (-2E-3 to -1E-3) *	-4E-3 (-5E-3 to -3E-3) *
	IS	-5E-4 (-6E-4 to -1E-4) * †	-4E-4 (-5E-4 to -2E-4) * †	-2E-4 (-4E-4 to -7E-5) *	-3E-4 (-4E-4 to -2E-4) *
	PCI/CABG	-2E-5 (-8E-5 to 1E-4)	-2E-4 (-2E-4 to -1E-4) *	6E-5 (-4E-5 to 2E-4)	-4E-5 (-1E-4 to 3E-5)
	death	-4E-3 (-5E-3 to -3E-3) * †	-9E-3 (-9E-3 to -8E-3) * †	-1E-3 (-1E-3 to -1E-3) *	-7E-3 (-8E-3 to -6E-3) *
	ACS/HF/IS	-6E-3 (-6E-3 to -5E-3) * †	-7E-3 (-7E-3 to -6E-3) * †	-3E-3 (-4E-3 to -2E-3) *	-7E-3 (-8E-3 to -6E-3) *
	ACS/HF/IS/death	-1E-2 (-1E-2 to -9E-3) * †	-2E-2 (-2E-2 to -2E-2) * †	-7E-3 (-9E-3 to -6E-3) *	-2E-2 (-2E-2 to -1E-2) *
A: AGE HEM  B: AGE HX	ACS	3E-4 (2E-4 to 4E-4) * †	1E-3 (1E-3 to 1E-3) * †	1E-4 (5E-5 to 2E-4) *	5E-4 (1E-4 to 9E-4) *
	HF	1E-3 (9E-4 to 2E-3) * †	3E-3 (3E-3 to 3E-3) * †	2E-3 (1E-3 to 2E-3) *	3E-3 (2E-3 to 5E-3) *
	IS	1E-4 (-4E-5 to 5E-4)	3E-4 (2E-4 to 4E-4) * †	1E-4 (-5E-5 to 3E-4)	3E-4 (1E-4 to 6E-4) *
	PCI/CABG	3E-4 (2E-4 to 4E-4) * †	1E-3 (1E-3 to 1E-3) * †	3E-4 (1E-4 to 5E-4) *	5E-4 (1E-4 to 9E-4) *
	death	-5E-4 (-1E-3 to 6E-4)	-4E-3 (-4E-3 to -3E-3) * †	1E-3 (8E-4 to 2E-3) *	-3E-3 (-4E-3 to -2E-3) *
	ACS/HF/IS	1E-3 (1E-3 to 2E-3) * †	3E-3 (3E-3 to 4E-3) * †	2E-3 (9E-4 to 3E-3) *	3E-3 (2E-3 to 5E-3) *
	ACS/HF/IS/death	-2E-4 (-1E-3 to 1E-3)	-2E-3 (-2E-3 to -1E-3) * †	-1E-4 (-1E-3 to 9E-4)	-3E-3 (-5E-3 to -5E-4) *
A: AGE HEM HX  B: AGE HX	ACS	1E-4 (1E-5 to 3E-4) *	1E-4 (-2E-5 to 4E-4)	-3E-6 (-3E-5 to 2E-5)	8E-5 (-3E-5 to 2E-4)
	HF	-1E-3 (-1E-3 to -8E-4) *	-1E-3 (-2E-3 to -1E-3) * †	-4E-4 (-8E-4 to 3E-5)	-1E-3 (-2E-3 to -5E-4) *
	IS	4E-5 (-1E-4 to 3E-4)	-6E-5 (-2E-4 to 2E-5)	4E-5 (-1E-4 to 2E-4)	7E-6 (-2E-4 to 2E-4)
	PCI/CABG	6E-5 (-5E-5 to 2E-4)	-2E-5 (-1E-4 to 1E-4)	5E-5 (-5E-5 to 2E-4)	2E-4 (2E-5 to 3E-4) *
	death	-1E-3 (-2E-3 to -6E-4) * †	-5E-3 (-5E-3 to -4E-3) * †	-1E-3 (-2E-3 to -6E-4) *	-4E-3 (-5E-3 to -2E-3) *
	ACS/HF/IS	-2E-3 (-2E-3 to -1E-3) *	-2E-3 (-2E-3 to -2E-3) * †	-4E-4 (-9E-4 to 6E-5)	-2E-3 (-3E-3 to -1E-3) *
	ACS/HF/IS/death	-4E-3 (-4E-3 to -4E-3) * †	-6E-3 (-6E-3 to -6E-3) * †	-2E-3 (-3E-3 to -1E-3) *	-6E-3 (-7E-3 to -4E-3) *

**Supplemental Table 9 (continued)**

Pred. Set	Outcome	$\Delta_S$ , Derivation Dataset		$\Delta_S$ , Validation Dataset	
		Women	Men	Women	Men
A: AGE HEM  B: HEM	ACS	2E-5 (-8E-5 to 2E-4)	-2E-4 (-2E-4 to -8E-5) * †	-6E-5 (-8E-5 to -4E-5) *	-1E-4 (-2E-4 to -2E-5) *
	HF	-2E-3 (-2E-3 to -1E-3) * †	-5E-4 (-9E-4 to -1E-4) *	-9E-4 (-1E-3 to -6E-4) *	1E-4 (-2E-4 to 4E-4)
	IS	-4E-4 (-4E-4 to -9E-5) * †	-2E-4 (-3E-4 to -1E-4) *	-3E-4 (-5E-4 to -1E-4) *	-6E-5 (-2E-4 to 6E-5)
	PCI/CABG	-8E-5 (-1E-4 to 2E-5)	-3E-4 (-3E-4 to -2E-4) * †	7E-5 (-2E-5 to 2E-4)	-2E-4 (-4E-4 to -1E-4) *
	death	-2E-3 (-3E-3 to -8E-4) *	-2E-3 (-2E-3 to -2E-3) * †	2E-4 (-4E-4 to 8E-4)	-2E-3 (-2E-3 to -1E-3) *
	ACS/HF/IS	-3E-3 (-3E-3 to -3E-3) * †	-1E-3 (-2E-3 to -7E-4) * †	-2E-3 (-2E-3 to -1E-3) *	-8E-4 (-1E-3 to -3E-4) *
	ACS/HF/IS/death	-5E-3 (-7E-3 to -3E-3) * †	-3E-3 (-3E-3 to -2E-3) * †	-4E-3 (-5E-3 to -3E-3) *	-4E-3 (-5E-3 to -3E-3) *
A: AGE HX  B: AGE	ACS	-2E-4 (-3E-4 to -2E-4) * †	-1E-3 (-1E-3 to -1E-3) * †	-2E-4 (-3E-4 to -8E-5) *	-5E-4 (-9E-4 to -1E-4) *
	HF	-4E-3 (-4E-3 to -3E-3) * †	-7E-3 (-7E-3 to -7E-3) * †	-3E-3 (-4E-3 to -2E-3) *	-7E-3 (-9E-3 to -6E-3) *
	IS	-6E-4 (-7E-4 to -5E-4) * †	-6E-4 (-7E-4 to -5E-4) * †	-3E-4 (-5E-4 to -2E-4) *	-6E-4 (-9E-4 to -4E-4) *
	PCI/CABG	-3E-4 (-4E-4 to -2E-4) * †	-2E-3 (-2E-3 to -1E-3) * †	-2E-4 (-3E-4 to -8E-5) *	-6E-4 (-1E-3 to -2E-4) *
	death	-3E-3 (-3E-3 to -3E-3) * †	-5E-3 (-5E-3 to -5E-3) * †	-2E-3 (-3E-3 to -2E-3) *	-4E-3 (-5E-3 to -3E-3) *
	ACS/HF/IS	-7E-3 (-7E-3 to -7E-3) * †	-1E-2 (-1E-2 to -1E-2) * †	-5E-3 (-6E-3 to -4E-3) *	-1E-2 (-1E-2 to -8E-3) *
	ACS/HF/IS/death	-1E-2 (-1E-2 to -1E-2) * †	-1E-2 (-1E-2 to -1E-2) * †	-7E-3 (-8E-3 to -6E-3) *	-1E-2 (-2E-2 to -1E-2) *
A: HEM HX  B: HEM	ACS	-2E-4 (-3E-4 to -1E-4) * †	-1E-3 (-1E-3 to -1E-3) * †	-9E-5 (-1E-4 to -7E-5) *	-5E-4 (-9E-4 to -2E-4) *
	HF	-4E-3 (-4E-3 to -3E-3) * †	-5E-3 (-5E-3 to -4E-3) * †	-3E-3 (-3E-3 to -2E-3) *	-4E-3 (-5E-3 to -3E-3) *
	IS	-2E-4 (-3E-4 to -9E-5) * †	-3E-4 (-4E-4 to -2E-4) * †	-3E-4 (-4E-4 to -1E-4) *	-2E-4 (-4E-4 to -4E-5) *
	PCI/CABG	-3E-4 (-4E-4 to -2E-4) * †	-2E-3 (-2E-3 to -1E-3) * †	-2E-4 (-3E-4 to -1E-4) *	-5E-4 (-9E-4 to -1E-4) *
	death	-1E-3 (-2E-3 to -9E-4) * †	-2E-3 (-2E-3 to -1E-3) * †	-1E-3 (-1E-3 to -6E-4) *	-7E-4 (-1E-3 to -2E-4) *
	ACS/HF/IS	-5E-3 (-5E-3 to -5E-3) * †	-6E-3 (-6E-3 to -6E-3) * †	-3E-3 (-4E-3 to -2E-3) *	-6E-3 (-7E-3 to -4E-3) *
	ACS/HF/IS/death	-6E-3 (-7E-3 to -5E-3) * †	-6E-3 (-6E-3 to -6E-3) * †	-4E-3 (-4E-3 to -3E-3) *	-5E-3 (-7E-3 to -4E-3) *
A: AGE HEM HX  B: AGE HEM	ACS	-2E-4 (-3E-4 to -6E-5) * †	-1E-3 (-1E-3 to -8E-4) * †	-1E-4 (-2E-4 to -5E-5) *	-4E-4 (-8E-4 to -6E-5) *
	HF	-2E-3 (-3E-3 to -2E-3) * †	-4E-3 (-5E-3 to -4E-3) * †	-2E-3 (-3E-3 to -2E-3) *	-5E-3 (-6E-3 to -4E-3) *
	IS	-6E-5 (-2E-4 to 7E-5)	-3E-4 (-4E-4 to -2E-4) * †	-1E-4 (-2E-4 to 6E-5)	-3E-4 (-6E-4 to -4E-5) *
	PCI/CABG	-2E-4 (-3E-4 to -8E-5) * †	-1E-3 (-1E-3 to -1E-3) *	-2E-4 (-3E-4 to -1E-4) *	-4E-4 (-8E-4 to 6E-5)
	death	-8E-4 (-2E-3 to -2E-4) * †	-1E-3 (-1E-3 to -8E-4) *	-2E-3 (-3E-3 to -2E-3) *	-3E-4 (-9E-4 to 1E-4)
	ACS/HF/IS	-3E-3 (-3E-3 to -3E-3) * †	-5E-3 (-6E-3 to -5E-3) * †	-2E-3 (-3E-3 to -2E-3) *	-6E-3 (-7E-3 to -4E-3) *
	ACS/HF/IS/death	-4E-3 (-5E-3 to -3E-3) * †	-4E-3 (-5E-3 to -4E-3) * †	-2E-3 (-2E-3 to -1E-3) *	-3E-3 (-4E-3 to -2E-3) *

**Supplemental Table 9:** Mean and 95% confidence interval of the statistic  $\Delta_S = S_A - S_B$ , where  $S_A$  is the right-censored Brier score for an outcome modeled with predictor set  $A$ , and  $S_B$  is the right-censored Brier score for an outcome modeled with predictor set  $B$ . Six predictor sets shown (AGE-HEM = age-hematology, AGE = age-only, AGE-HX = age-history, AGE-HEM-HX = age-hematology-history, HEM = hematology-only, HEM-HX = hematology-history). Observations and predictions are compared at 3 years after a patient's entry into study. Note that  $\Delta_S < 0$  means that predictor set  $A$  performs better than predictor set  $B$ . This is in contrast to Table 6 and Supp. Table 8, where  $\Delta_C < 0$  means predictor set  $A$  performs worse than predictor set  $B$ . An asterisk ( \* ) denotes that  $\Delta_S$  is significantly different from zero. A cross ( † ) next to a derivation-set result denotes that that  $\Delta_S$  is also significantly different from zero in the validation set, and the effect is in the same direction as in the

derivation dataset, i.e. the result in the derivation set is corroborated by the result in the validation set). There were no cases where a validation-set result was significant, but in the opposite direction of a significant derivation-set result. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke; PCI/CABG = percutaneous coronary intervention / coronary artery bypass graft

**Supplemental Table 10: Comparison of AGE-HEM and AGE predictor sets, according to C-index, performance on outcomes derived from ICD10 codes**

Pred. Set	Outcome	ICD10		AI-adjudicated	
		Women	Men	Women	Men
A: AGE HEM	ACS	0.007 (-0.009 to 0.024)	0.016 (-0.008 to 0.039)	0.019 (0.005 to 0.033) *	0.003 (-0.012 to 0.019)
	HF	0.075 (0.055 to 0.095) *	0.118 (0.091 to 0.145) *	0.086 (0.072 to 0.100) *	0.092 (0.071 to 0.113) *
B: AGE	IS	0.056 (0.021 to 0.093) *	0.006 (-0.034 to 0.047)	0.024 (0.009 to 0.039) *	0.029 (0.009 to 0.050) *
	ACS/HF/IS	0.048 (0.033 to 0.063) *	0.084 (0.063 to 0.105) *	0.048 (0.038 to 0.058) *	0.055 (0.042 to 0.069) *

**Supplemental Table 10:** Mean and 95% confidence interval of the statistic  $\Delta_C = C_A - C_B$ , where  $C_A$  is the C-index of an outcome modeled with the hematology-age predictor set, and  $C_B$  is the C-index for an outcome modeled with the age-only predictor set. Two predictor sets shown (AGE-HEM = age-hematology, AGE = age-only). An asterisk ( \* ) denotes that  $\Delta_C$  is significantly different from zero. Models are trained on derivation cohort. Performance on validation dataset composed of ICD10-derived outcomes is under column "ICD10". Performance on validation dataset composed of AI-adjudicated outcomes is shown for comparison under column "AI-adjudicated". ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke

**Supplemental Table 11: Comparison of AGE-HEM and AGE predictor sets, according to Brier score, performance on outcomes derived from ICD10 codes**

Pred. Set	Outcome	ICD10		AI-adjudicated	
		Women	Men	Women	Men
A: AGE HEM	ACS	-4E-5 (-7E-5 to -2E-5) *	-2E-5 (-9E-5 to 4E-5)	-4e-5 (-5e-5 to -2e-5) *	5e-6 (-7e-5 to 8e-5)
	HF	-6E-4 (-9E-4 to -2E-4) *	-2E-3 (-3E-3 to -1E-3) *	-1e-3 (-2e-3 to -1e-3) *	-4e-3 (-5e-3 to -3e-3) *
B: AGE	IS	2E-4 (6E-5 to 3E-4) *	-4E-5 (-8E-5 to -1E-5) *	-2e-4 (-4e-4 to -7e-5) *	-3e-4 (-4e-4 to -2e-4) *
	ACS/HF/IS	-1E-3 (-1E-3 to -4E-4) *	-3E-3 (-4E-3 to -3E-3) *	-3e-3 (-4e-3 to -2e-3) *	-7e-3 (-8e-3 to -6e-3) *

**Supplemental Table 11:** Mean and 95% confidence interval of the statistic  $\Delta_S = S_A - S_B$ , where  $S_A$  is the right-censored Brier score for an outcome modeled with hematology-age, and  $S_B$  is the right-censored Brier score for an outcome modeled with age-only predictor set. Two predictor sets shown (AGE-HEM = age-hematology, AGE = age-only). Observations and predictions are compared at 3 years after a patient's entry into study. Note that  $\Delta_S < 0$  means that hematology-age performs better than age-only predictor set. An asterisk ( \* ) denotes that  $\Delta_S$  is significantly different from zero. Models are trained on derivation cohort. Performance on validation dataset composed of ICD10-derived outcomes is under column "ICD10". Performance on validation dataset composed of AI-adjudicated outcomes is shown for comparison under column "AI-adjudicated". ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke

**Supplemental Table 12. Comparison of predictor sets, using Charlson comorbidity index, according to C-index**

A: AGE HEM HX	Outcome	$\Delta_c$ , Derivation Dataset		$\Delta_c$ , Validation Dataset	
		Women	Men	Women	Men
B: AGE HX	death	0.045 (0.028 to 0.059) * †	0.049 (0.047 to 0.051) * †	0.023 (0.016 to 0.029) *	0.040 (0.029 to 0.049) *
	ACS/HF/IS/death	0.044 (0.025 to 0.055) * †	0.039 (0.037 to 0.054) * †	0.028 (0.022 to 0.034) *	0.032 (0.025 to 0.039) *

**Supplemental Table 12:** Mean and 95% confidence interval of the statistic  $\Delta_C = C_A - C_B$ , where  $C_A$  is the C-index of an outcome modeled with the age-hematology-history predictor set, and  $C_B$  is the C-index for an outcome modeled with the age-history predictor set. Two predictor sets shown (AGE-HEM-HX = age-hematology-history, AGE-HX = age-history). An asterisk ( \* ) denotes that  $\Delta_C$  is significantly different from zero. A cross ( † ) next to a derivation-set result denotes that that  $\Delta_C$  is also significantly different from zero in the validation set, and the effect is in the same direction as in the derivation dataset, i.e., the result in the derivation set is corroborated by the result in the validation set. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke

**Supplemental Table 13. Comparison of predictor sets, using Charlson comorbidity index, according to 3-year Brier score**

A: AGE HEM HX	Outcome	$\Delta_s$ , Derivation Dataset		$\Delta_s$ , Validation Dataset	
		Women	Men	Women	Men
B: AGE HX	death	-3E-3 (-4E-3 to -2E-3) * †	-5E-3 (-5E-3 to -5E-3) * †	-1E-3 (-2E-3 to -9E-4) *	-4E-3 (-5E-3 to -3E-3) *
	ACS/HF/IS/death	-7E-3 (-9E-3 to -5E-3) * †	-7E-3 (-9E-3 to -7E-3) * †	-8E-3 (-9E-3 to -7E-3) *	-7E-3 (-9E-3 to -6E-3) *

**Supplemental Table 13:** Mean and 95% confidence interval of the statistic  $\Delta_S = S_A - S_B$ , where  $S_A$  is the right-censored Brier score for an outcome modeled with hematology-age-history, and  $S_B$  is the right-censored Brier score for an outcome modeled with age-history predictor set. Two predictor sets shown (AGE-HEM-HX = age-hematology-history, AGE-HX = age-history). Observations and predictions are compared at 3 years after a patient's entry into study. Note that  $\Delta_S < 0$  means that age-hematology-history performs better than the age-history predictor set. An asterisk ( \* ) denotes that  $\Delta_S$  is significantly different from zero. A cross ( † ) next to a derivation-set result denotes that that  $\Delta_S$  is also significantly different from zero in the validation set, and the effect is in the same direction as in the derivation dataset, i.e., the result in the derivation set is corroborated by the result in the validation set. There were no cases where a validation-set result was significant, but in the opposite direction of a significant derivation-set result. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke

**Supplemental Table 14. Comparison of AGE-HEM and AGE predictor sets, according to C-index, performance on population with no prior AI-adjudicated CVD events**

Pred. Set	Outcome	Event-free members of validation cohort		Entire validation cohort	
		Women	Men	Women	Men
A: AGE HEM	ACS	0.012 (-0.003 to 0.028)	-0.002 (-0.020 to 0.015)	0.019 (0.005 to 0.033) *	0.003 (-0.012 to 0.019)
	HF	0.088 (0.071 to 0.105) *	0.091 (0.063 to 0.120) *	0.086 (0.072 to 0.100) *	0.092 (0.071 to 0.113) *
	IS	0.014 (-0.003 to 0.030)	0.030 (0.005 to 0.054) *	0.024 (0.009 to 0.039) *	0.029 (0.009 to 0.050) *
	PCI/CABG	0.001 (-0.022 to 0.025)	-0.007 (-0.025 to 0.013)	0.030 (0.007 to 0.055) *	0.005 (-0.013 to 0.025)
B: AGE	death	0.061 (0.046 to 0.078) *	0.093 (0.076 to 0.110) *	0.065 (0.051 to 0.079) *	0.091 (0.077 to 0.105) *
	ACS/HF/IS	0.041 (0.030 to 0.053) *	0.046 (0.029 to 0.062) *	0.048 (0.038 to 0.058) *	0.055 (0.042 to 0.069) *
	ACS/HF/IS/death	0.056 (0.045 to 0.066) *	0.070 (0.057 to 0.082) *	0.058 (0.049 to 0.068) *	0.070 (0.060 to 0.080) *

**Supplemental Table 14:** Mean and 95% confidence interval of the statistic  $\Delta_C = C_A - C_B$ , where  $C_A$  is the C-index of an outcome modeled with the hematology-age predictor set, and  $C_B$  is the C-index for an outcome modeled with the age-only predictor set. Two predictor sets shown (AGE-HEM = age-hematology, AGE = age-only). An asterisk ( \*) denotes that  $\Delta_C$  is significantly different from zero. Models are trained on derivation cohort. Performance on the event-free fraction of the validation dataset under the left two columns; performance on entire validation dataset is under the right two columns. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke; PCI/CABG = percutaneous coronary intervention / coronary artery bypass graft

**Supplemental Table 15. Comparison of AGE-HEM and AGE predictor sets, according to Brier score, performance on population with no prior AI-adjudicated CVD events**

Pred. Set	Outcome	Event-free members of validation cohort		Entire validation cohort	
		Women	Men	Women	Men
A: AGE HEM	ACS	-3e-5 (-4e-5 to -1e-5) *	2e-5 (-4e-5 to 9e-5)	-4e-5 (-5e-5 to -2e-5) *	5e-6 (-7e-5 to 8e-5)
	HF	-6e-4 (-1e-3 to -3e-4) *	-2e-3 (-3e-3 to -2e-3) *	-1e-3 (-2e-3 to -1e-3) *	-4e-3 (-5e-3 to -3e-3) *
	IS	-1e-4 (-3e-4 to 2e-5)	-2e-4 (-3e-4 to -2e-4) *	-2e-4 (-4e-4 to -7e-5) *	-3e-4 (-4e-4 to -2e-4) *
	PCI/CABG	1e-4 (8e-6 to 3e-4) *	-4e-5 (-1e-4 to 3e-5)	6e-5 (-4e-5 to 2e-4)	-4e-5 (-1e-4 to 3e-5)
B: AGE	death	-9e-4 (-1e-3 to -7e-4) *	-5e-3 (-7e-3 to -4e-3) *	-1e-3 (-1e-3 to -1e-3) *	-7e-3 (-8e-3 to -6e-3) *
	ACS/HF/IS	-1e-3 (-2e-3 to -8e-4) *	-4e-3 (-5e-3 to -4e-3) *	-3e-3 (-4e-3 to -2e-3) *	-7e-3 (-8e-3 to -6e-3) *
	ACS/HF/IS/death	-5e-3 (-6e-3 to -4e-3) *	-1e-2 (-1e-2 to -1e-2) *	-7e-3 (-9e-3 to -6e-3) *	-2e-2 (-2e-2 to -1e-2) *

**Supplemental Table 15:** Mean and 95% confidence interval of the statistic  $\Delta_S = S_A - S_B$ , where  $S_A$  is the right-censored Brier score for an outcome modeled with hematology-age, and  $S_B$  is the right-censored Brier score for an outcome modeled with age-only predictor set. Two predictor sets shown (AGE-HEM = age-hematology, AGE = age-only). Observations and predictions are compared at 3 years after a patient's entry into study. Note that  $\Delta_S < 0$  means that hematology-age performs better than age-only predictor set. An asterisk ( \*) denotes that  $\Delta_S$  is significantly different from zero. Models are trained on derivation cohort. Performance on the event-free fraction of the validation dataset is under the left two columns; performance on entire validation dataset is under the right two columns. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke; PCI/CABG = percutaneous coronary intervention / coronary artery bypass graft

**Supplemental Table 16. Comparison of AGE-HEM and AGE predictor sets, according to C-index, performance on population with no prior AI-adjudicated CVD events and no ICD10-derived history of CVD disease**

Pred. Set	Outcome	Disease-free members of validation cohort		Entire validation cohort	
		Women	Men	Women	Men
A: AGE-HEM	ACS	0.017 (-0.003 to 0.035)	-0.008 (-0.028 to 0.012)	0.019 (0.005 to 0.033) *	0.003 (-0.012 to 0.019)
	HF	0.104 (0.081 to 0.126) *	0.093 (0.049 to 0.134) *	0.086 (0.072 to 0.100) *	0.092 (0.071 to 0.113) *
	IS	0.013 (-0.004 to 0.030)	0.020 (-0.005 to 0.047)	0.024 (0.009 to 0.039) *	0.029 (0.009 to 0.050) *
	PCI/CABG	0.004 (-0.024 to 0.036)	-0.006 (-0.029 to 0.018)	0.030 (0.007 to 0.055) *	0.005 (-0.013 to 0.025)
B: AGE	death	0.073 (0.054 to 0.093) *	0.107 (0.084 to 0.131) *	0.065 (0.051 to 0.079) *	0.091 (0.077 to 0.105) *
	ACS/HF/IS	0.045 (0.032 to 0.059) *	0.045 (0.023 to 0.070) *	0.048 (0.038 to 0.058) *	0.055 (0.042 to 0.069) *
	ACS/HF/IS/death	0.063 (0.051 to 0.075) *	0.077 (0.061 to 0.094) *	0.058 (0.049 to 0.068) *	0.070 (0.060 to 0.080) *

**Supplemental Table 16:** Mean and 95% confidence interval of the statistic  $\Delta_C = C_A - C_B$ , where  $C_A$  is the C-index of an outcome modeled with the hematology-age predictor set, and  $C_B$  is the C-index for an outcome modeled with the age-only predictor set. Two predictor sets shown (AGE-HEM = age-hematology, AGE = age-only) An asterisk ( \* ) denotes that  $\Delta_C$  is significantly different from zero. Models are trained on derivation cohort. Performance on the disease-free fraction of the validation dataset under the left two columns; performance on entire validation dataset is under the right two columns. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke; PCI/CABG = percutaneous coronary intervention / coronary artery bypass graft

**Supplemental Table 17. Comparison of AGE-HEM and AGE predictor sets, according to Brier score, performance on population with no prior AI-adjudicated CVD events and no ICD10-derived history of CVD disease**

Pred. Set	Outcome	Disease-free members of validation cohort		Entire validation cohort	
		Women	Men	Women	Men
A: AGE-HEM	ACS	-2e-5 (-3e-5 to -5e-6) *	-2e-5 (-7e-5 to 3e-5)	-4e-5 (-5e-5 to -2e-5) *	5e-6 (-7e-5 to 8e-5)
	HF	-3e-4 (-6e-4 to -4e-5) *	-2e-3 (-2e-3 to -1e-3) *	-1e-3 (-2e-3 to -1e-3) *	-4e-3 (-5e-3 to -3e-3) *
	IS	-1e-4 (-3e-4 to -4e-5) *	-2e-4 (-2e-4 to -1e-4) *	-2e-4 (-4e-4 to -7e-5) *	-3e-4 (-4e-4 to -2e-4) *
	PCI/CABG	4e-5 (1e-5 to 8e-5) *	-8e-5 (-1e-4 to -2e-5) *	6e-5 (-4e-5 to 2e-4)	-4e-5 (-1e-4 to 3e-5)
B: AGE	death	-7e-4 (-9e-4 to -6e-4) *	-4e-3 (-5e-3 to -3e-3) *	-1e-3 (-1e-3 to -1e-3) *	-7e-3 (-8e-3 to -6e-3) *
	ACS/HF/IS	-8e-4 (-1e-3 to -3e-4) *	-3e-3 (-4e-3 to -3e-3) *	-3e-3 (-4e-3 to -2e-3) *	-7e-3 (-8e-3 to -6e-3) *
	ACS/HF/IS/death	-4e-3 (-5e-3 to -3e-3) *	-1e-2 (-1e-2 to -8e-3) *	-7e-3 (-9e-3 to -6e-3) *	-2e-2 (-2e-2 to -1e-2) *

**Supplemental Table 17:** Mean and 95% confidence interval of the statistic  $\Delta_S = S_A - S_B$ , where  $S_A$  is the right-censored Brier score for an outcome modeled with hematology-age, and  $S_B$  is the right-censored Brier score for an outcome modeled with age-only predictor set. Two predictor sets shown (AGE-HEM = age-hematology, AGE = age-only). Observations and predictions are compared at 3 years after a patient's entry into study. Note that  $\Delta_S < 0$  means that hematology-age performs better than age-only predictor set. An asterisk ( \* ) denotes that  $\Delta_S$  is significantly different from zero. Models are trained on derivation cohort. Performance on the disease-free fraction of the validation dataset is under the left two columns; performance on entire validation dataset is under the right two columns. ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke; PCI/CABG = percutaneous coronary intervention / coronary artery bypass graft

**Supplemental Table 18. Comparison of Cox proportional-hazards model with pooled-cohort equations for 3-year ASCVD risk, according to cumulative-dynamic AUC**

Pred. Set	$\Delta_A$ , Internal Test Set		$\Delta_A$ , External Validation Set	
	Women	Men	Women	Men
AGE-HEM	0.040 (0.034 to 0.047) * †	0.086 (0.081 to 0.090) *	0.071 (0.022 to 0.119) *	0.039 (-0.009 to 0.089)

**Supplemental Table 18:** Mean and 95% confidence interval of the statistic  $\Delta_A = A_{COX} - A_{PCE}$ , where  $A_{COX}$  is the 3-year cumulative-dynamic AUC of the Cox proportional-hazards model for outcome ACS/IS/death, and  $A_{PCE}$  is the cumulative-dynamic AUC for 3-year PCE. An asterisk ( \* ) denotes that  $\Delta_A$  is significantly different from zero. A cross ( † ) next to a derivation-set result denotes that  $\Delta_A$  is also significantly different from zero in the validation set, and the effect is in the same direction as in the derivation dataset, i.e. the result in the derivation set is corroborated by the result in the validation set).

**Supplemental Table 19. Comparison of Cox proportional-hazards model with pooled-cohort equations for 3-year ASCVD risk, according to Brier score**

Pred. Set	$\Delta_S$ , Internal Test Set		$\Delta_S$ , External Validation Set	
	Women	Men	Women	Men
AGE-HEM	-2e-3 (-2e-3 to -2e-3) *	-4e-3 (-4e-3 to -4e-3) *	-1e-3 (-6e-3 to 5e-3)	-1e-3 (-1e-2 to 7e-3)

**Supplemental Table 19:** Mean and 95% confidence interval of the statistic  $\Delta_S = S_{COX} - S_{PCE}$ , where  $S_{COX}$  is the 3-year Brier score of the Cox proportional-hazards model for outcome ACS/IS/death, and  $S_{PCE}$  is the 3-year Brier score for 3-year PCE. An asterisk ( \* ) denotes that  $\Delta_S$  is significantly different from zero. Note that  $\Delta_S < 0$  means that the Cox proportional-hazards model performs better than the 3-year pooled-cohort equations.



**Supplemental Table 20. Comparison of random survival forest model to Cox proportional hazards on the basis of C-index**

Pred. Set	Outcome	Superiority of RSF to Cox	
		Women	Men
HEM	ACS	0.023	0.016
	HF	0.018	0.011
	IS	0.003	0.007
	PCI/CABG	0.050	0.007
	death	0.022	0.009
	ACS/HF/IS	0.016	0.007
	ACS/HF/IS/death	0.022	0.009
AGE HEM	ACS	0.012	0.013
	HF	0.015	0.008
	IS	0.000	-0.014
	PCI/CABG	0.020	-0.002
	death	0.012	0.001
	ACS/HF/IS	0.010	0.006
	ACS/HF/IS/death	0.017	0.006
AGE HEM HX	ACS	0.002	0.011
	HF	0.020	0.004
	IS	0.000	-0.008
	PCI/CABG	0.015	0.002
	death	0.008	0.003
	ACS/HF/IS	0.008	0.003
	ACS/HF/IS/death	0.010	0.004
AGE HX	ACS	0.009	0.004
	HF	-0.001	0.000
	IS	-0.006	-0.009
	PCI/CABG	0.022	0.003
	death	-0.003	-0.004
	ACS/HF/IS	-0.004	-0.001
	ACS/HF/IS/death	-0.003	-0.002
AGE	ACS	0.024	0.000
	HF	0.010	-0.005
	IS	-0.009	0.004
	PCI/CABG	0.021	0.003
	death	-0.002	-0.006
	ACS/HF/IS	-0.008	-0.003
	ACS/HF/IS/death	-0.007	-0.004

**Supplemental Table 20:** Comparison of random survival forest to penalized Cox proportional hazards. Metric is the quantity  $\Delta_C = C_{RSF} - C_{COX}$ .  $C_{RSF}$  is the mean test-set C-index obtained during  $k$ -fold cross-validation.  $C_{RSF}$  is measured using the best hyperparameter set of 32 sets, selecting on the basis of mean test-set C-index.  $C_{COX}$  is the mean C-index obtained by repeated  $k$ -fold cross-validation. Five predictor sets shown (AGE-HEM = age-

hematology, AGE = age-only, AGE-HX = age-history, AGE-HEM-HX = age-hematology-history, HEM = hematology-only). ACS = acute coronary syndrome; HF = heart failure; IS = ischemic stroke; PCI/CABG = percutaneous coronary intervention / coronary artery bypass graft

