SUPPLEMENTARY APPENDIX

The contents of the supplementary appendix are aimed to provide a deeper understanding towards the analyses performed for this study. It enables replication of the models, through outcome and prognostic factor definitions and exact specification of the developed models.

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eTable 1: Completed TRIPOD checklist

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	4
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	5
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	5
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	5
	5b	D;V	Describe eligibility criteria for participants.	5
	5c	D;V	Give details of treatments received, if relevant.	n/a
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6; eTable 3
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	n/a
Predictors	7a	D;V	Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured.	6; eTable 2
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	n/a
Sample size	8	D;V	Explain how the study size was arrived at.	6
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	7
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	6-7
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	6-7
	10c	V	For validation, describe how the predictions were calculated.	7
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	7
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	n/a
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	7
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	5,Table 1; eFigure 2
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	eFigure 1

Section/Topic	Item		Checklist Item	Page
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 1
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 1; eTable 4; eFigure 5
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	eFigure 1
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	eFigure 3
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	eTable 5-6
	15b	D	Explain how to use the prediction model.	11
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	8-9
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	n/a
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	12
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	10-11
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	10-11; Table 2
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	11-12
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Web calculator available with publication; eFigure 7
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	14

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V.

eTable 2: Timing and sources of prognostic factors

Prognostic Factor	Definitions	Timing of measure
Age (years)		At cohort entry
Gender		-
Smoking status	https://www.caliberresearch.org/portal/show/smoking_status_composite	Most recent value recorded in the year prior to cohort entry
Excess alcohol	https://www.caliberresearch.org/portal/show/alcohol_drinker_composite	At any time prior to cohort entry
Index of multiple deprivation		
Ethnicity		-
Index MI subtype	https://www.caliberresearch.org/portal/show/phenotype_mi	Index MI
Diabetes	https://www.caliberresearch.org/portal/show/phenotype_diabetes	At any time prior to cohort entry
History of MI (prior to index MI)	https://www.caliberresearch.org/portal/show/phenotype_mi	At any time prior to index MI
History of stroke	https://www.caliberresearch.org/portal/show/ischaemic_stroke_gprd https://www.caliberresearch.org/portal/show/ischaemic_stroke_hes https://www.caliberresearch.org/portal/show/stroke_nos_gprd https://www.caliberresearch.org/portal/show/stroke_nos_hes	At any time prior to cohort entry
Previous revascularisation	https://www.caliberresearch.org/portal/show/pci_gprd https://www.caliberresearch.org/portal/show/pci_opcs https://www.caliberresearch.org/portal/show/cabg_gprd https://www.caliberresearch.org/portal/show/cabg_opcs	At any time prior to cohort entry
History of atrial fibrillation	https://www.caliberresearch.org/portal/show/phenotype_af	At any time prior to cohort entry
History of heart failure	https://www.caliberresearch.org/portal/show/phenotype_hf	At any time prior to cohort entry
History of peripheral arterial disease	https://www.caliberresearch.org/portal/show/phenotype_pad	At any time prior to cohort entry
Chronic anaemia	https://www.caliberresearch.org/portal/show/chronicanaemia_gprd https://www.caliberresearch.org/portal/show/chronicanaemia_hes	At any time prior to cohort entry
History of hospitalised bleed	**ICD-10** I60 I61 I62 K250 K282 K284 K286 K290 K252 K254 K256 K260 K625 K920 K921 K922 K262 K264 K266 K270 P261 R040 R041 R048 K272 K274 K276 K280 R049 H356 H431 H450	At any time prior to cohort entry
History of peptic ulcer	https://www.caliberresearch.org/portal/show/pepticulcer_gprd https://www.caliberresearch.org/portal/show/pepticulcer_hes	At any time prior to cohort entry
Bleeding diatheses and coagulation disorders	**ICD-10 codes** D66X D67X D680 D681 D691 D692 D693 D694 D682 D683 D684 D685 D695 D696 D698 D699 D686 D688 D689 D690 **Read codes** D304.00 D305.00 D307.00 D307y00 D307z00 Dyu3000 D310.00 D310z00 D311.00 D312.00 Dyu3100 D313.12 D313000 D313012 Dyu3200 D314.00 D314y00 D314z00 D31y.00 Dyu3300 D31X.00 D300.00 D300.12 D301.00 D301.12 D302.00 D302.11 D303.00 D30A.00 D30..00 D30z.00 42P2.00 42P2.11 D313.00 D313111 D313300 D313y00 D313z00 D313z11 D314100 D315.00	At any time prior to cohort entry

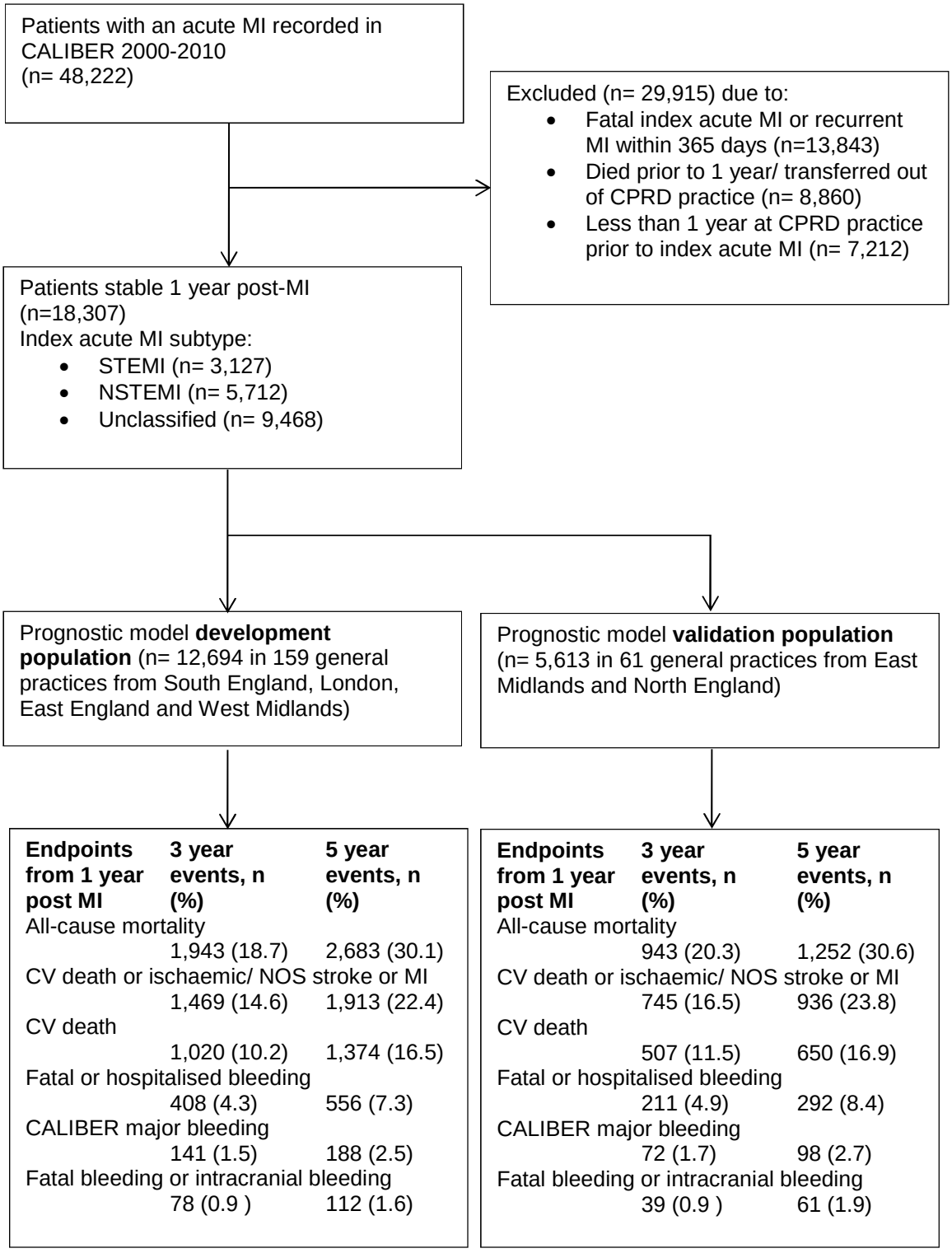
History of COPD	https://www.caliberresearch.org/portal/show/copd_gprd https://www.caliberresearch.org/portal/show/copd_hes	At any time prior to cohort entry
Recent hospitalisation for acute COPD	https://www.caliberresearch.org/portal/show/copd_hes	In the year prior to cohort entry
Liver disease	https://www.caliberresearch.org/portal/show/liver_charlson_gprd https://www.caliberresearch.org/portal/show/liver_charlson_hes https://www.caliberresearch.org/portal/show/cirrhosis_gprd https://www.caliberresearch.org/portal/show/cirrhosis_hes https://www.caliberresearch.org/portal/show/pbc_diag_gprd https://www.caliberresearch.org/portal/show/pbc_diag_hes	At any time prior to cohort entry
History of renal disease	https://www.caliberresearch.org/portal/show/renal_gprd https://www.caliberresearch.org/portal/show/renal_hes	At any time prior to cohort entry
Recent hospitalisation for acute renal disease	https://www.caliberresearch.org/portal/show/renal_hes	In the year prior to cohort entry
History of non-metastatic cancer	https://www.caliberresearch.org/portal/show/cancer_gprd https://www.caliberresearch.org/portal/show/cancer_hes	At any time prior to cohort entry
History of metastatic cancer	https://www.caliberresearch.org/portal/show/cancer_gprd https://www.caliberresearch.org/portal/show/cancer_hes	At any time prior to cohort entry
History of dementia	https://www.caliberresearch.org/portal/show/dementia_gprd https://www.caliberresearch.org/portal/show/dementia_hes	At any time prior to cohort entry
BMI SBP (mmHg) DBP (mmHg) Pulse rate (bpm) Haemoglobin (g/dL) Total cholesterol (mmol/L) HDL cholesterol (mmol/L) Creatinine (mol/l) eGFR (ml/min)	https://www.caliberresearch.org/portal/show/bmi https://www.caliberresearch.org/portal/show/bp_gprd https://www.caliberresearch.org/portal/show/bp_gprd https://www.caliberresearch.org/portal/show/pulse_rate_gprd https://www.caliberresearch.org/portal/show/haemoglobin_gprd https://www.caliberresearch.org/portal/show/total_chol_serum_gprd https://www.caliberresearch.org/portal/show/HDL_serum_gprd https://www.caliberresearch.org/portal/show/crea_gprd https://www.caliberresearch.org/portal/show/egfr_ckdepi_gprd	Most recent value recorded in the year prior to cohort entry

eTable 3: Defining three bleeding endpoints using codes in linked electronic health records

Endpoint	ICD-10 codes
Fatal or hospitalised bleeding	In hospital admissions (HES) OR death registry(ONS): I60 I61 I62 K250 K252 K254 K256 K260 K262 K264 K266 K270 K272 K274 K276 K280 K282 K284 K286 K290 K625 K920 K921 K922 P261 R040 R041 R048 R049 H356 H431 H450
CALIBER major bleeding	In hospital admissions (HES): I60 I61 I62 In death registry (ONS): I60 I61 I62 K250 K252 K254 K256 K260 K262 K264 K266 K270 K272 K274 K276 K280 K282 K284 K286 K290 K625 K920 K921 K922 P261 R040 R041 R048 R049 H356 H431 H450 **Or** all-cause mortality within 7 days of a hospital admission for any of the above codes **Or** any of the above codes in hospital admissions with primary admission and hospitalisation >14days **Or** any of the above codes in hospital admissions with a transfusion code in primary care (Read codes 7L14.00, 7L14000, 7L14100, 7L14300, 7L14311, 7L14y00, 7L14z00, TAy0.00, TB1y000, ZV58200) or hospital (OPCS codes X33, X331, X332, X333, X338, X339) within 30 days
Fatal or intracranial bleeding	In hospital admissions (HES): I60 I61 I62 In death registry(ONS): I60 I61 I62 K250 K252 K254 K256 K260 K262 K264 K266 K270 K272 K274 K276 K280 K282 K284 K286 K290 K625 K920 K921 K922 P261 R040 R041 R048 R049 H356 H431 H450 **Or** all-cause mortality within 7 days of a hospital admission for any of the above codes

Note: the prefix of the code can identify the bleeding location: I=Intracranial, K=Gastrointestinal, P=pulmonary, R=respiratory, H= Eye; Fatal or hospitalised bleeding included fatal bleeding or hospitalisation of any duration with bleeding as a primary or secondary reason for admission; CALIBER major bleeding included fatal or intracranial bleeding, bleeding as a primary cause of hospitalisation with length of stay > 14 days or bleedings requiring transfusion. Bleeding requiring transfusion were identified as bleedings with a relevant transfusion record in either primary or secondary care within 30 days following the bleeding; Fatal or intracranial bleeding included fatal bleeding or intracranial bleeding only. Bleedings were considered fatal if there was a bleeding code recorded as the underlying cause of death or if a patient died from any cause within 7 days of hospitalised bleeding;

eFigure 1: Study population flow diagram, endpoints and 3 & 5 year event rates



Endpoints from 1 year post MI	3 year events, n (%)	5 year events, n (%)
All-cause mortality	1,943 (18.7)	2,683 (30.1)
CV death or ischaemic/ NOS stroke or MI	1,469 (14.6)	1,913 (22.4)
CV death	1,020 (10.2)	1,374 (16.5)
Fatal or hospitalised bleeding	408 (4.3)	556 (7.3)
CALIBER major bleeding	141 (1.5)	188 (2.5)
Fatal bleeding or intracranial bleeding	78 (0.9)	112 (1.6)

Endpoints from 1 year post MI	3 year events, n (%)	5 year events, n (%)
All-cause mortality	943 (20.3)	1,252 (30.6)
CV death or ischaemic/ NOS stroke or MI	745 (16.5)	936 (23.8)
CV death	507 (11.5)	650 (16.9)
Fatal or hospitalised bleeding	211 (4.9)	292 (8.4)
CALIBER major bleeding	72 (1.7)	98 (2.7)
Fatal bleeding or intracranial bleeding	39 (0.9)	61 (1.9)

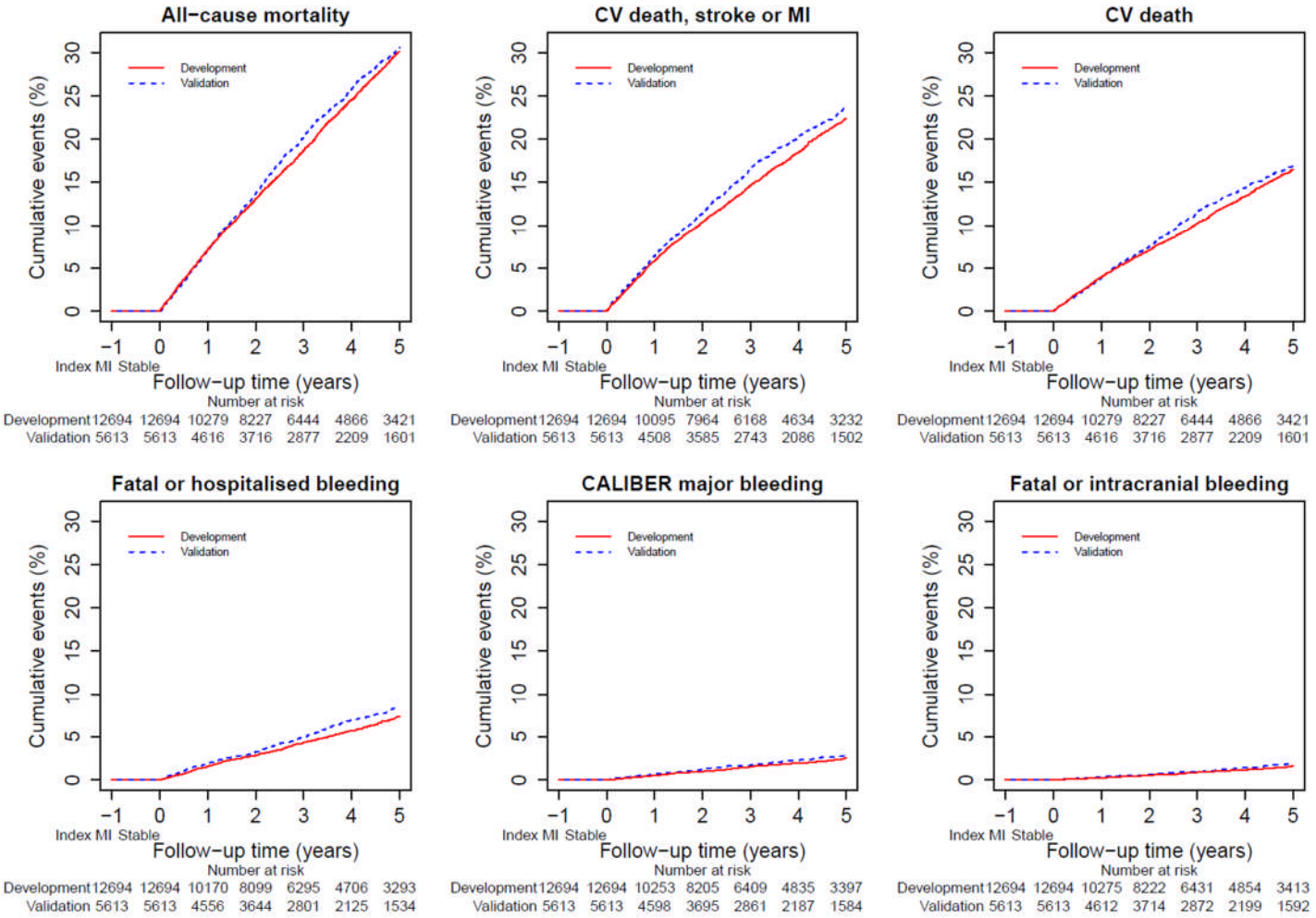
Note: MI= myocardial infarction, STEMI=ST-elevation myocardial infarction, NSTEMI= non-ST-elevation myocardial infarction, NOS=not otherwise specified, CV=cardiovascular

eTable 4: Patient characteristics at index acute MI discharge and 1 year post-index acute MI in the development (n=12,694) and validation (n=5,613) cohorts

	Development (n=12,694)		Validation (n=5,613)	
	At index acute MI discharge	**1 year post-MI**	**At index acute MI**	**1 year post-MI**
Age	69.1 (12.7)	70.1 (12.7)	68.1 (12.8)	69.1 (12.8)
Behaviours				
Smoking status				
Ex-smoker	40.1	49.3	40.3	50.0
Non-smoker	42	36.7	38.7	34.2
Smoker	17.9	14.0	21.1	15.8
Alcohol abuse	9.8	10.8	14.3	15.4
Cardiovascular diseases				
Revascularisation (PCI)	24.8	43.5	18.8	33.0
Heart failure	18.2	23.5	21.4	28.0
Atrial fibrillation	14.9	18.0	14.8	17.9
Stroke	6.0	6.9	7.0	8.1
Peripheral arterial disease	8.2	9.8	11	13.1
Diabetes				
Type 1	1.3	1.2	0.9	0.9
Type 2	15.2	16.7	15.5	17
Unspecified	1.2	1.5	1.4	1.7
Renal disease	8.7	13.6	9.5	14.8
Non-cardiovascular diseases				
COPD	7.8	9.1	10.9	12.8
Liver disease	0.3	0.4	0.5	0.5
Non-metastatic cancer	12.9	14.4	11.3	13.2
Metastatic cancer	0.8	1.0	0.7	1.2
Dementia	0.8	1.3	1.4	2.0
Chronic anaemia	11	14.3	14	17.9
Peptic ulcer	6.6	7.3	9.3	10.2
Bleeding diatheses and coagulation disorders	0.8	1.1	0.9	1.1
Hospitalised bleeding	4.3	6.5	5.7	8.2
Biomarkers				
BMI (Continuous)	28.0 (5.0)	27.8 (5.1)	27.9 (5.2)	27.7 (5.1)
BMI (Categorical)				
Underweight	1.1	1.5	1.6	1.8
Normal	27.1	28.7	27.9	28.4
Overweight	41.8	41.2	42.1	42.2
Obese	30.1	28.6	28.4	27.7
SBP (mmHg)	145 (16.3)	133 (18.6)	144 (17.0)	132 (18.4)
Haemoglobin (g/dL)	13.9 (1.62)	13.4 (1.6)	13.9 (1.61)	13.3 (1.6)
White blood cell count (10^9/L)	7.69 (2.19)	7.60 (2.3)	7.72 (2.19)	7.68 (2.3)
Total cholesterol (mmol/L)	5.32 (1.16)	4.17 (1.0)	5.38 (1.14)	4.17 (1.0)
HDL cholesterol (mmol/L)	1.34 (0.40)	1.28 (0.4)	1.33 (0.37)	1.26 (0.4)
Creatinine (mol/l) Median (IQR)	95 (83, 110)	98 (84, 114)	97 (85, 113)	99 (86, 117)

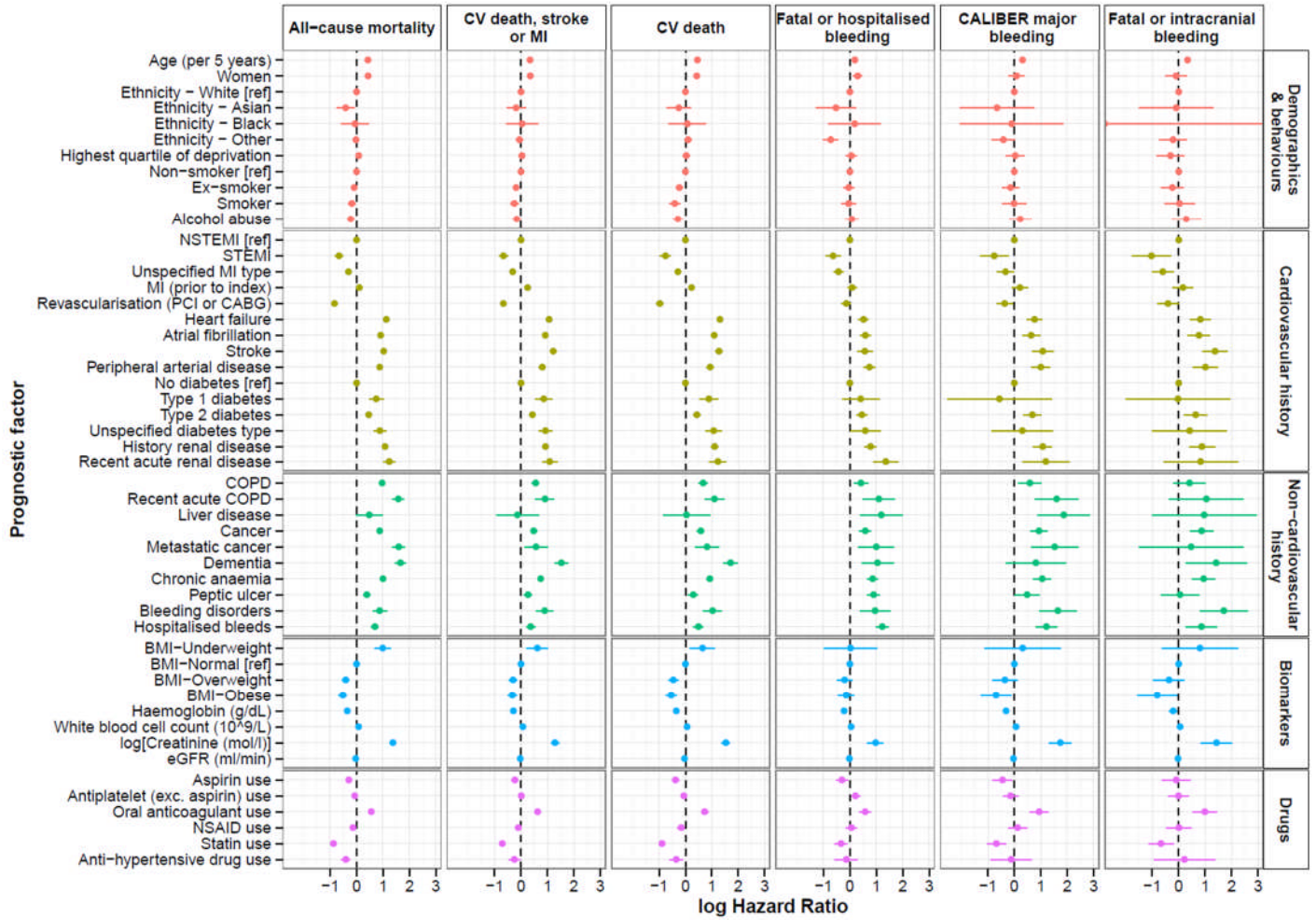
Note: Categorical prognostic factors are presented as %, continuous prognostic factors are presented as mean (SD) unless stated otherwise

eFigure 2: Comparison of all-cause mortality, cardiovascular and bleeding events in patents included in the development (n=12,694) and validation (n=5,613) cohorts



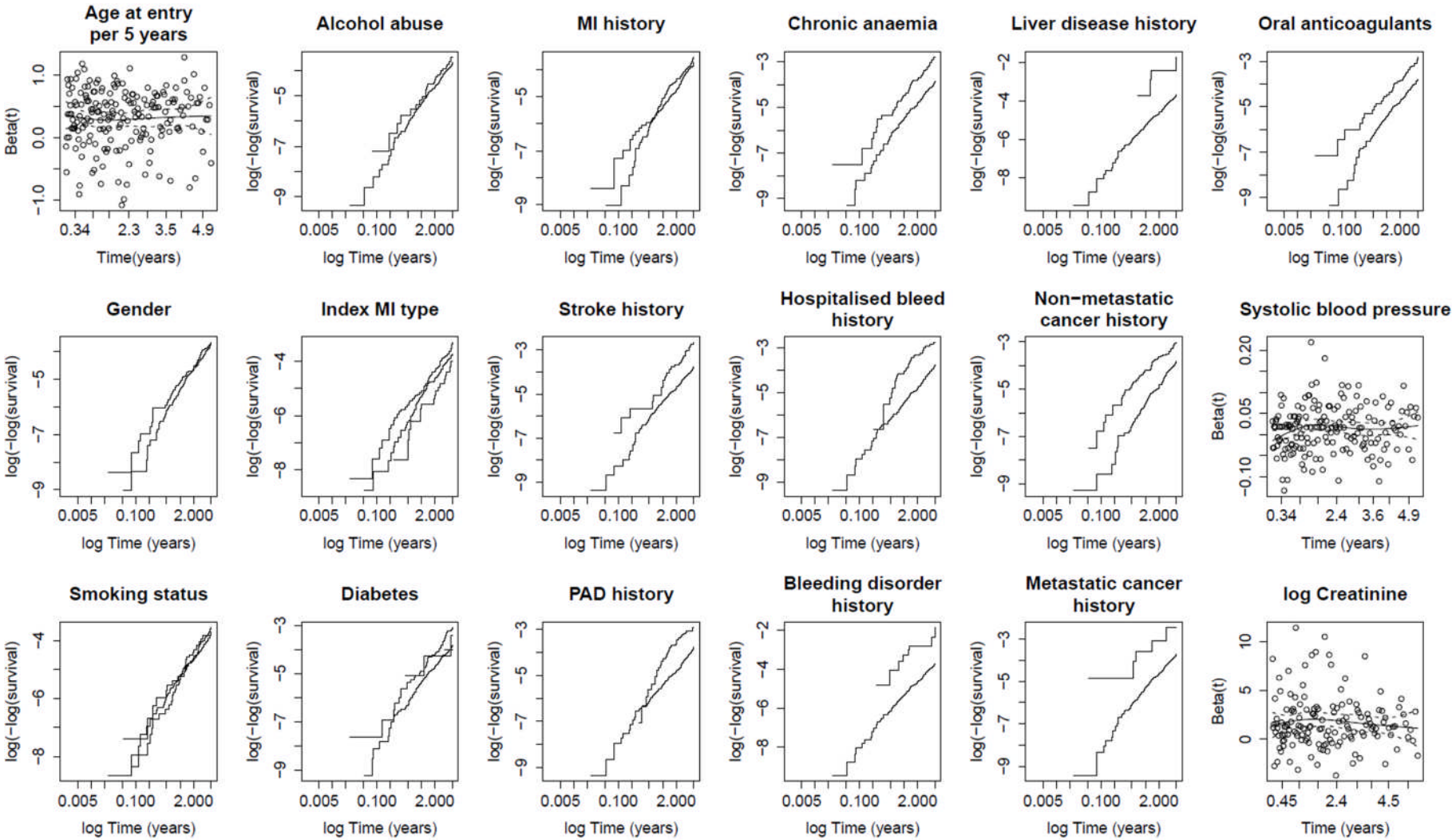
Note: CV= cardiovascular, MI=myocardial infarction

eFigure 3: Univariable effects of prognostic factors on 5 year all-cause mortality, cardiovascular and bleeding endpoints



Note: CV= cardiovascular, MI= myocardial infarction, NSTEMI= non-ST-elevation myocardial infarction, STEMI= ST-elevation myocardial infarction, COPD= chronic obstructive pulmonary disease, BMI= body mass index, eGFR= estimated glomerular filtration rate, NSAID= non-steroidal anti-inflammatory drugs; (log hazards compared with reference group or per unit increase for continuous prognostic factors and 95% confidence intervals)

eFigure 4: Univariable proportional hazards assumption checks for the CALIBER major bleeding outcome



Note: For continuous variables, Beta(t) is a time dependent coefficient and should remain constant over time if the proportional hazards assumption have not been violated **.** For categorical variables, proportional hazards have not been violated if the log(-log(survival)) curves remain parallel over time.; MI= myocardial infarction; PAD= peripheral arterial disease

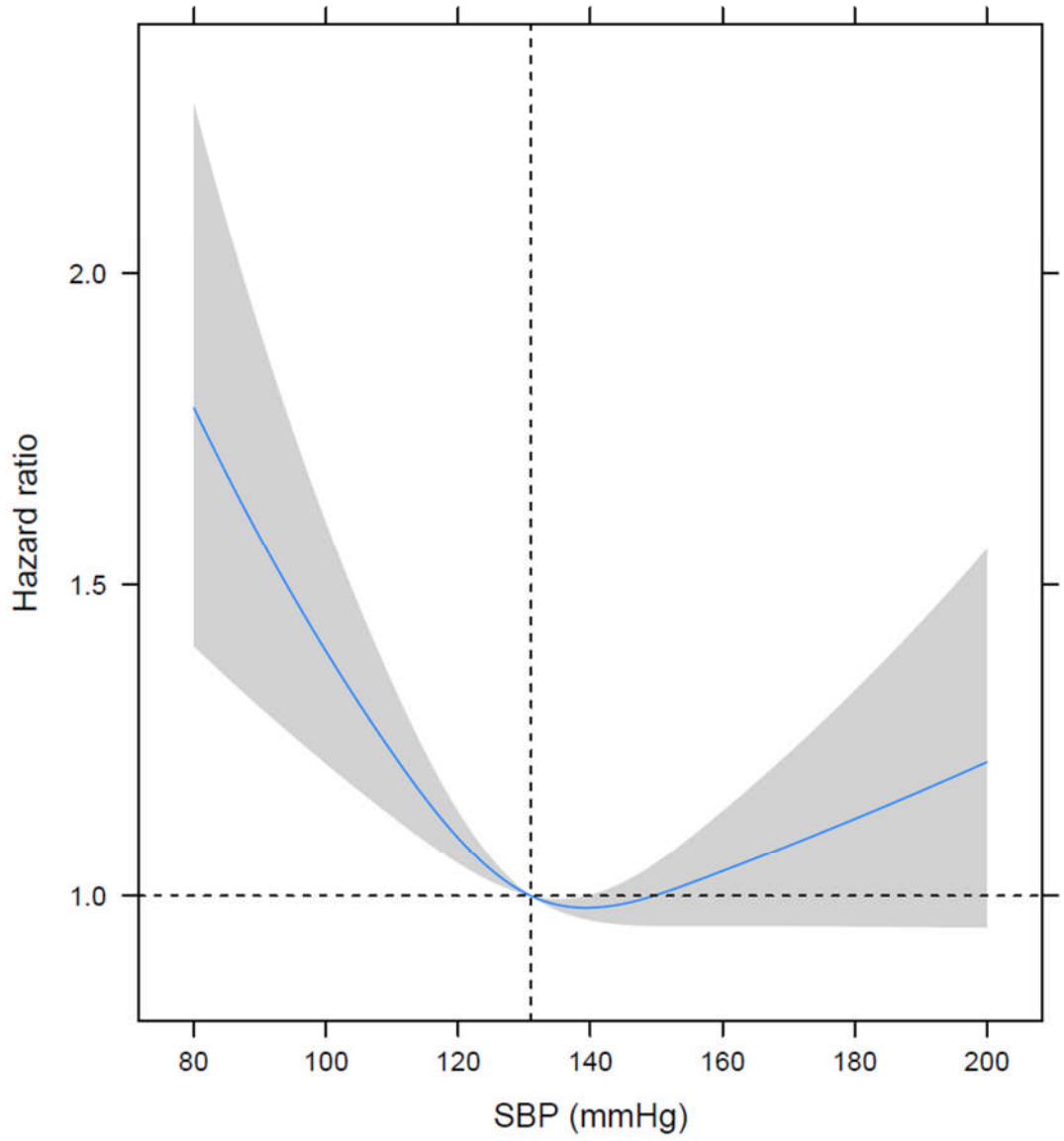
eTable 5: Multivariable model prognostic hazard ratios and 95% confidence intervals for all-cause mortality, cardiovascular and bleeding endpoints

Prognostic factor (measured at 1 year post-MI)	Endpoint					
	All-cause mortality	Cardiovascular death, stroke or MI	Cardiovascular death	CALIBER major bleeding	Fatal or hospitalised bleeding	Fatal bleeding or intracranial bleeding
Age (per 5 years)	1.38 (1.35, 1.42)	1.28 (1.24, 1.32)	1.39 (1.34, 1.45)	1.3 (1.19, 1.42)	1.14 (1.09, 1.19)	1.35 (1.20, 1.52)
Women	0.89 (0.81, 0.98)	0.89 (0.79, 0.99)	0.85 (0.75, 0.97)	0.85 (0.61, 1.2)	1.15 (0.95, 1.4)	0.54 (0.34, 0.85)
Ethnicity						
White [ref]	1	NA	1	NA	1	NA
Asian	0.96 (0.68, 1.36)	NA	1.07 (0.68, 1.68)	NA	0.68 (0.32, 1.44)	NA
Black	1.19 (0.7, 2.04)	NA	1.28 (0.63, 2.6)	NA	1.20 (0.45, 3.22)	NA
Other	1.16 (1.05, 1.28)	NA	1.26 (1.1, 1.44)	NA	0.58 (0.43, 0.77)	NA
Smoking status						
Non-smoker [ref]	1	1	1	1	1	1
Ex-smoker	1.02 (0.93, 1.12)	0.91 (0.82, 1.01)	0.9 (0.79, 1.02)	0.88 (0.63, 1.23)	0.96 (0.79, 1.17)	0.73 (0.47, 1.14)
Smoker	1.47 (1.28, 1.7)	1.25 (1.06, 1.48)	1.22 (0.99, 1.5)	1.42 (0.87, 2.32)	1.23 (0.92, 1.64)	1.44 (0.77, 2.68)
Alcohol abuse	1.24 (1.07, 1.43)	1.25 (1.07, 1.47)	1.23 (1.01, 1.5)	1.69 (1.08, 2.65)	1.28 (0.97, 1.68)	1.80 (1.02, 3.19)
Index acute MI type						
NSTEMI [ref]	1	1	1	1	1	1
STEMI	0.81 (0.7, 0.93)	0.74 (0.63, 0.87)	0.74 (0.61, 0.91)	0.67 (0.39, 1.16)	0.67 (0.5, 0.91)	0.51 (0.24, 1.06)
Unspecified	0.88 (0.81, 0.97)	0.78 (0.7, 0.86)	0.82 (0.73, 0.93)	0.84 (0.61, 1.15)	0.78 (0.65, 0.95)	0.61 (0.40, 0.91)
MI (prior to index acute MI)	1.07 (0.98, 1.16)	1.23 (1.12, 1.35)	1.2 (1.08, 1.34)	1.18 (0.88, 1.59)	1.04 (0.87, 1.23)	1.14 (0.77, 1.68)
Previous revascularisation	0.69 (0.63, 0.76)	0.72 (0.64, 0.8)	0.61 (0.53, 0.7)	NA	NA	0.87 (0.56, 1.34)
Heart failure	1.47 (1.35, 1.6)	1.57 (1.42, 1.74)	1.74 (1.55, 1.97)	NA	NA	1.34 (0.88, 2.04)
Atrial fibrillation	1.23 (1.13, 1.34)	1.33 (1.2, 1.47)	1.41 (1.26, 1.59)	NA	NA	0.85 (0.51, 1.42)
Stroke	1.41 (1.26, 1.58)	1.86 (1.64, 2.11)	1.73 (1.49, 2)	1.6 (1.06, 2.43)	1.13 (0.84, 1.51)	2.28 (1.38, 3.78)
Peripheral arterial disease	1.48 (1.33, 1.64)	1.45 (1.28, 1.64)	1.6 (1.38, 1.84)	1.55 (1.06, 2.27)	1.41 (1.11, 1.79)	1.64 (1.01, 2.69)
Diabetes						
No diabetes	1	1	1	1	1	1

Prognostic factor (measured at 1 year post-MI)	Endpoint					
	All-cause mortality	**Cardiovascular death, stroke or MI**	**Cardiovascular death**	**CALIBER major bleeding**	**Fatal or hospitalised bleeding**	**Fatal bleeding or intracranial bleeding**
Type 1 diabetes	2.33 (1.75, 3.09)	2.33 (1.7, 3.2)	2.44 (1.68, 3.52)	0.55 (0.08, 4)	1.48 (0.73, 3)	0.87 (0.12, 6.40)
Type 2 diabetes	1.22 (1.11, 1.35)	1.18 (1.05, 1.32)	1.15 (1, 1.33)	1.49 (1.06, 2.09)	1.29 (1.05, 1.59)	1.48 (0.95, 2.30)
Unspecified diabetes	2.44 (1.93, 3.1)	2.34 (1.79, 3.07)	2.89 (2.13, 3.92)	1.07 (0.33, 3.41)	1.62 (0.9, 2.89)	1.31 (0.31, 5.45)
Renal disease	1.23 (1.1, 1.37)	NA	NA	NA	NA	NA
COPD	1.62 (1.45, 1.8)	NA	1.23 (1.04, 1.44)	NA	NA	NA
Liver disease	NA	NA	NA	3.94 (1.4, 11.11)	NA	NA
Non-metastatic cancer	1.31 (1.19, 1.44)	NA	NA	1.48 (1.04, 2.12)	1.26 (1.01, 1.56)	1.49 (0.95, 2.34)
Metastatic cancer	2.32 (1.81, 2.98)	NA	NA	2.19 (0.86, 5.58)	NA	NA
Dementia	2.03 (1.64, 2.53)	2.03 (1.56, 2.64)	2.16 (1.62, 2.87)	NA	NA	NA
Chronic anaemia	1.13 (1.02, 1.25)	NA	NA	1.42 (0.99, 2.03)	1.40 (1.13, 1.73)	1.42 (0.89, 2.25)
Peptic ulcer	NA	NA	1.02 (0.85, 1.24)	NA	1.75 (1.37, 2.24)	NA
Bleeding diatheses or coagulation disorders	NA	1.3 (0.95, 1.79)	NA	2.02 (0.94, 4.32)	NA	2.49 (0.95, 6.48)
Hospitalised bleeding	NA	0.84 (0.71, 1)	0.85 (0.69, 1.03)	1.82 (1.2, 2.78)	2.01 (1.56, 2.58)	NA
BMI						
Underweight	1.91 (1.43, 2.53)	1.6 (1.11, 2.3)	1.65 (1.09, 2.5)	NA	NA	NA
Normal [ref]	1	1	1	NA	NA	NA
Overweight	0.93 (0.82, 1.05)	0.95 (0.84, 1.08)	0.92 (0.78, 1.08)	NA	NA	NA
Obese	1 (0.88, 1.15)	1.05 (0.91, 1.22)	1.02 (0.85, 1.24)	NA	NA	NA
White blood cell count (10^9/L)	1.06 (1.03, 1.08)	1.05 (1.02, 1.07)	1.05 (1.02, 1.08)	NA	NA	NA
Haemoglobin (g/dL)	0.88 (0.85, 0.92)	0.91 (0.88, 0.95)	0.89 (0.85, 0.93)	NA	NA	NA
log Creatinine (µmol/l)	1.35 (1.15, 1.59)	1.49 (1.25, 1.77)	1.72 (1.41, 2.1)	2.15 (1.29, 3.57)	1.44 (1.05, 1.97)	NA
Cholesterol ratio (HDL:total)	1.58 (0.92, 2.71)	1.46 (0.82, 2.59)	1.56 (0.77, 3.15)	NA	NA	NA
Antiplatelet	NA	NA	NA	NA	1.23 (1.03, 1.47)	NA
Oral anticoagulant	NA	NA	NA	1.74 (1.19, 2.52)	1.49 (1.17, 1.9)	1.89 (1.08, 3.33)

Note: All models are adjusted for systolic blood pressure using restricted cubic splines. Functions are shown in **eTable 5**; MI=myocardial infarction, NSTEMI= non-ST-elevation myocardial infarction, STEMI= ST-elevation myocardial infarction, COPD= chronic obstructive pulmonary disease, HDL= high-density lipoprotein

eFigure 5: U-shaped association of systolic blood pressure and 5 year cardiovascular death, stroke or MI events [n=12,694, events=1,913]



Note: MI= myocardial infarction; SBP= systolic blood pressure

eTable 6: Linear predictor functions for systolic blood pressure in the multivariable models

Endpoint	Function
All-cause mortality	$0.011 \times SBP - 3.566 \times 10^{-6} \times \max(SBP-110,0)^3 + 6.562 \times 10^{-6} \times \max(SBP-131,0)^3 - 2.996 \times 10^{-6} \times \max(SBP-156,0)^3$
Cardiovascular death, stroke or MI	$0.012 \times SBP - 5.619 \times 10^{-6} \times \max(SBP-110,0)^3 + 1.034 \times 10^{-5} \times \max(SBP-131,0)^3 - 4.720 \times 10^{-6} \times \max(SBP-156,0)^3$
Cardiovascular death	$0.015 \times SBP - 6.383 \times 10^{-6} \times \max(SBP-110,0)^3 + 1.174 \times 10^{-5} \times \max(SBP-131,0)^3 - 5.362 \times 10^{-6} \times \max(SBP-156,0)^3$
CALIBER major bleeding	$0.006^* SBP - 5.722 \times 10^{-6} \times \max(SBP-110,0)^3 + 1.0529 \times 10^{-5} \times \max(SBP-131,0)^3 - 4.807 \times 10^{-6} \times \max(SBP-156,0)^3$
Fatal or hospitalised bleeding	$0.010 \times SBP - 6.231 \times 10^{-6} \times \max(SBP-110,0)^3 + 1.146 \times 10^{-5} \times \max(SBP-131,0)^3 - 5.234 \times 10^{-6} \times \max(SBP-156,0)^3$
Fatal bleeding or intracranial bleeding	$0.002 \times SBP - 5.176 \times 10^{-6} \times \max(SBP-110,0)^3 + 9.524 \times 10^{-6} \times \max(SBP-131,0)^3 - 4.348 \times 10^{-6} \times \max(SBP-156,0)^3$

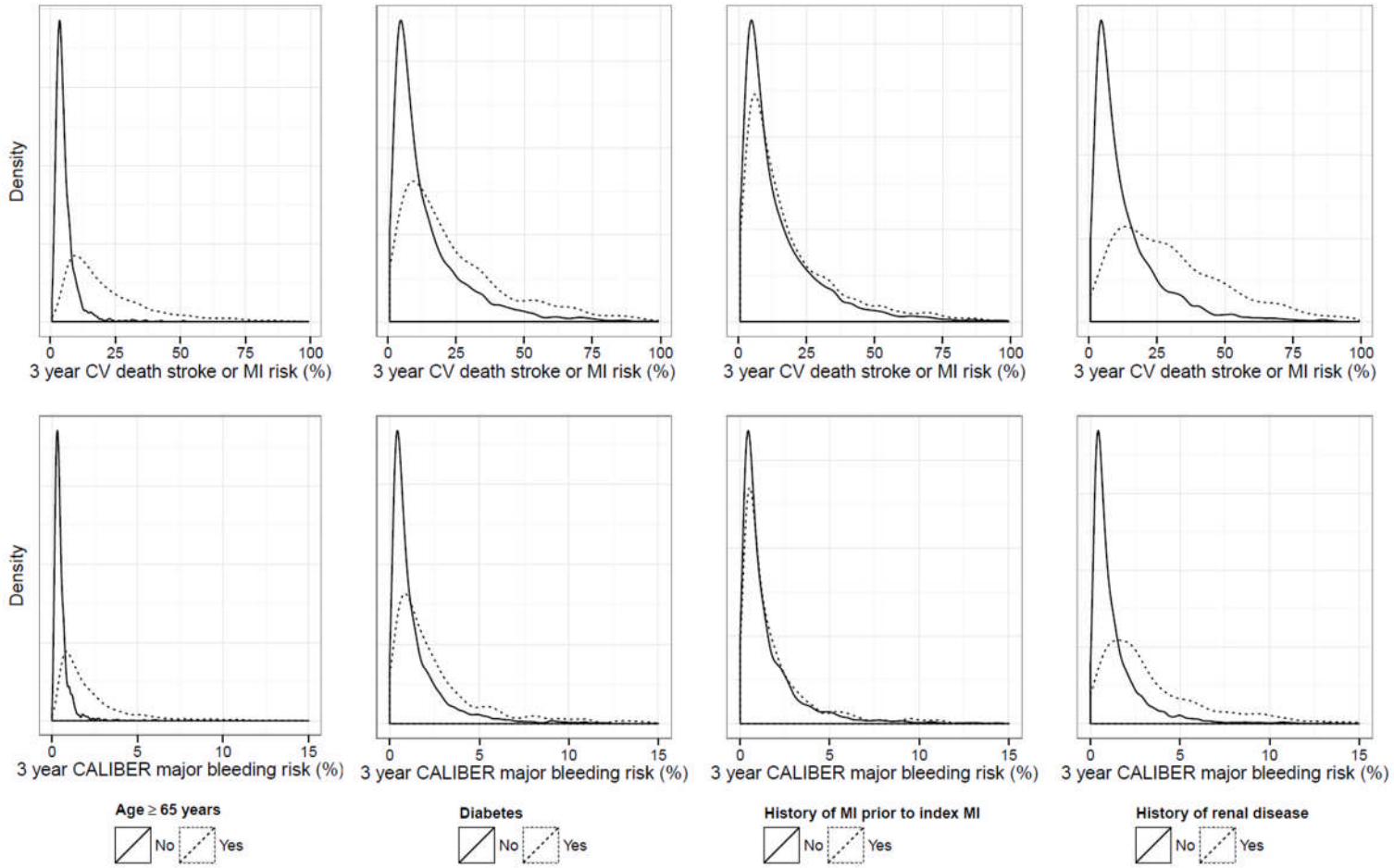
Note: Systolic blood pressure was modelled using restricted cubic splines with 3 knots in the multivariable models. The functions in this table described the estimated relationship between systolic blood pressure and the studied endpoints

eTable 7: Percentages of patients in the 4 risk groups from applying the 16%, 50% and 84% cut-points of the linear predictors calculated with the development cohort for each endpoint

		Risk Group			
Endpoint	**Cohort**	**Highest**	**High**	**Low**	**Lowest**
CV death stroke MI	Development	16.0	34.0	34.0	16.0
	Validation	17.7	34.2	33.6	14.5
Fatal or intracranial bleeding	Development	16.0	34.0	34.0	16.0
	Validation	16.1	33.7	34.9	15.4
CALIBER major bleeding	Development	16.0	34.0	34.0	16.0
	Validation	16.7	33.5	34.6	15.3
Hospitalised bleeding	Development	16.0	34.0	34.0	16.0
	Validation	18.5	33.5	33.2	14.8

Note: Development cohort (n=12,694), Validation cohort (n=5,613)

eFigure 6: Overlap of 3 year predicted risks based on multivariable models in those with and without categorical risk factors: age≥ 65, diabetes, history of MI and renal disease (used to define high risk in the PEGASUS-TIMI 54 trial)



Note: Each panel shows the distribution of predicted 3-year CV or bleeding risks in patients with and without 4 binary indicators of high CV risk (Age, diabetes, MI history, renal disease). The dotted curve is the distribution of risk for patients with the high risk factor and the solid curve is the distribution of risk without the high risk factor. We demonstrate that these 'high risk' factors alone are insufficient to separate patients who are truly at higher and lower risks. CV= cardiovascular; MI= myocardial infarction