

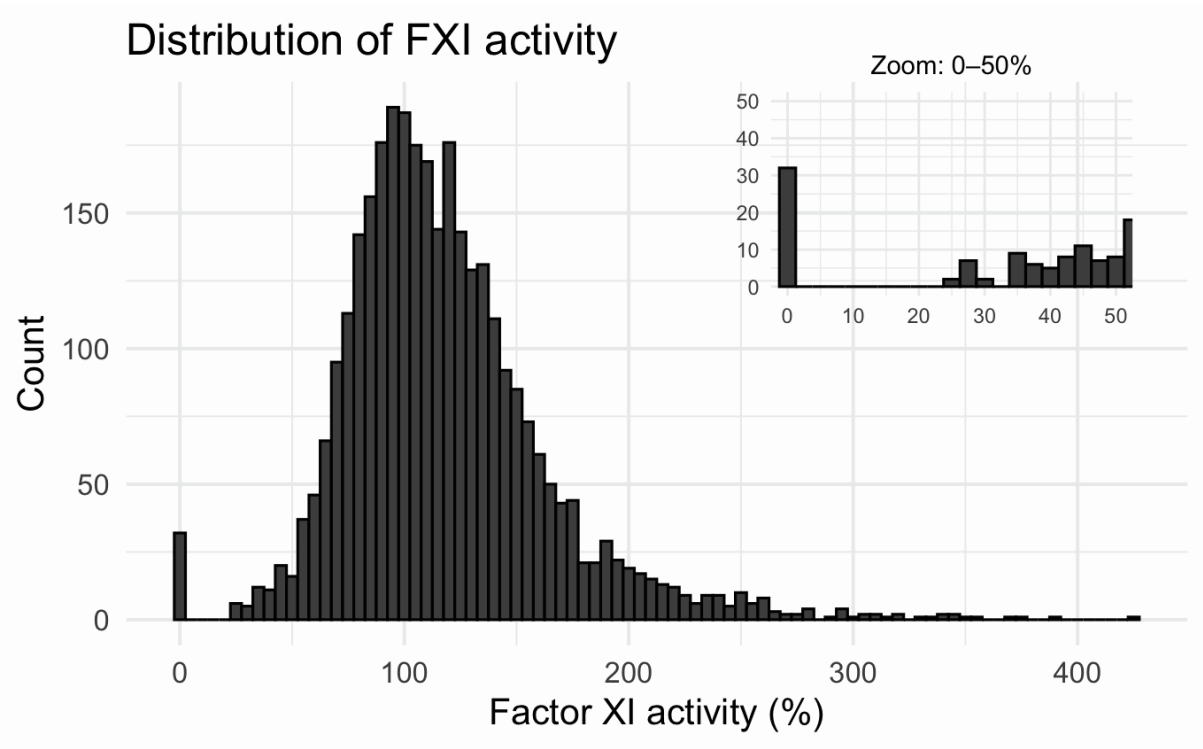
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Supplemental information

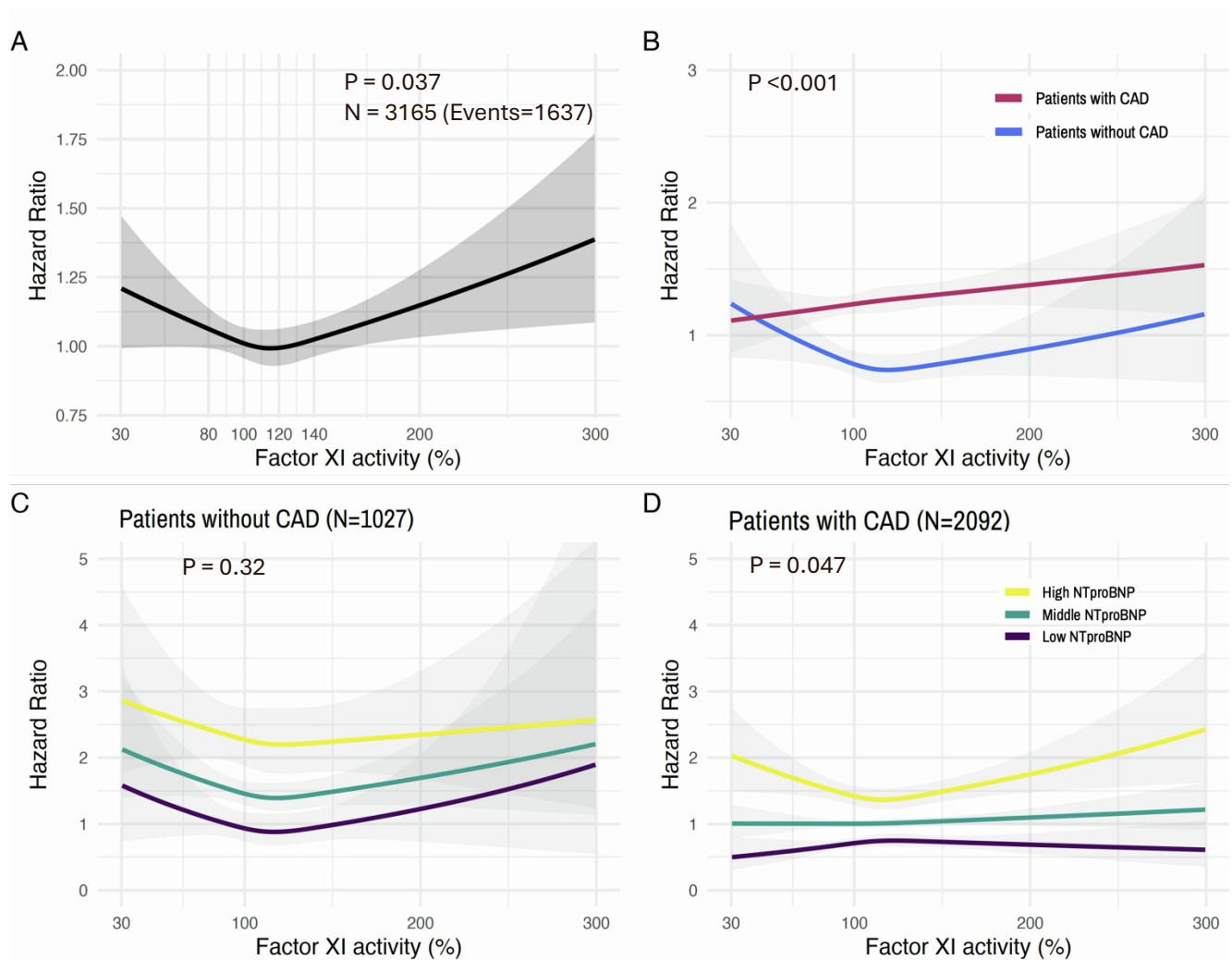
Non-linear association of coagulation factor XI with mortality

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Supplementary Figures



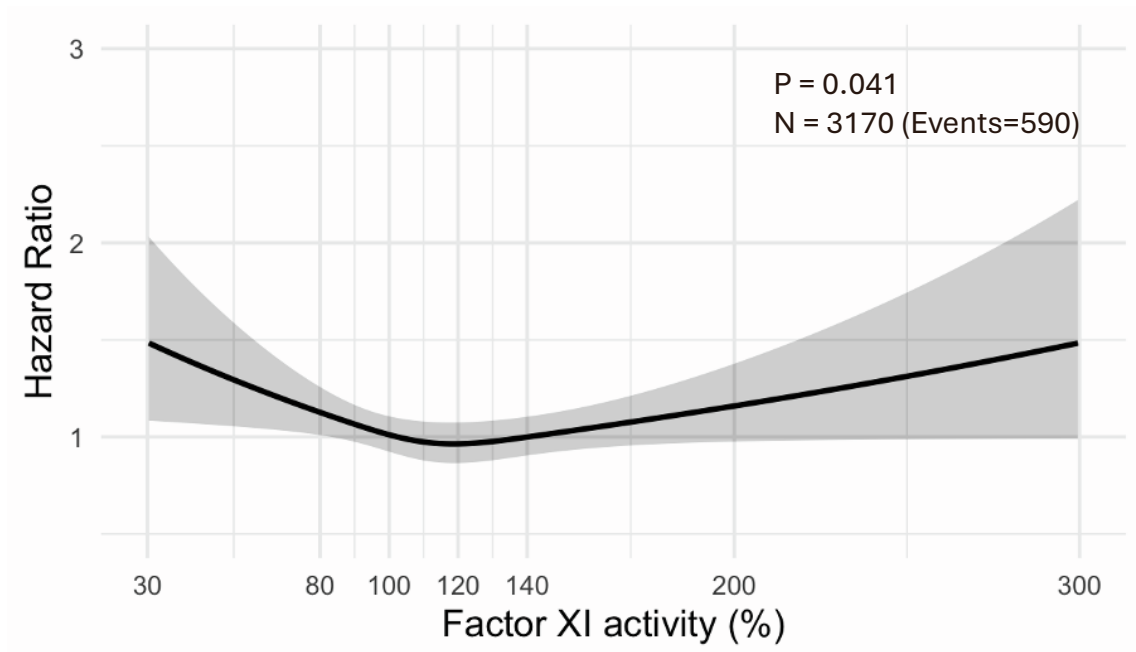
Supplementary Figure 1: Distribution of factor XI activity in the study cohort, related to Table 1, Figure 1 and STAR Methods



Supplementary Figure 2: U-shaped and subgroup-specific associations between factor XI activity and all-cause mortality using fully adjusted models, related to Figure 1 and STAR Methods

Panel A shows a non-linear association in the overall cohort. Panel B displays distinct associations by presence of coronary artery disease (CAD). Panels C and D show the effect modification by NT-proBNP tertiles in participants without (C) and with (D) CAD, respectively

All models are adjusted for age, sex, BMI, non-HDL cholesterol, mean arterial pressure, and estimated glomerular filtration rate (eGFR, CKD-EPI using Cystatin C). In the model displayed on panel B, an additional interaction with NT-proBNP was used. Shaded areas represent 95% confidence intervals.



Supplementary Figure 3: Non-linear association between factor XI activity and major adverse cardiac event (MACE) related mortality, related to Figure 1 and STAR Methods

Supplementary Table 1: Baseline characteristics and medication use stratified by angiography-confirmed coronary artery disease (CAD), related to Figure 1 and STAR Methods.

	without CAD	with CAD	p value
n	1028	2095	
Age, years	62 [54, 69]	64 [57, 71]	<0.001
Female, n (%)	481 (46.8)	481 (23.0)	<0.001
BMI, kg/m²	26.9 [24.5, 29.8]	27.1 [24.8, 29.7]	0.549
Smoking status			<0.001
never, n (%)	515 (50.1)	622 (29.7)	
former, n (%)	333 (32.4)	1048 (50.0)	
active, n (%)	180 (17.5)	425 (20.3)	
Diabetes (ADA), n (%)	232 (22.6)	761 (36.3)	<0.001
eGFR (CKD-EPI cystatin C), mL/min/1.73 m²	82.8 [69.0, 96.7]	80.1 [64.9, 93.1]	<0.001
High-sensitive C-reactive protein, mg/L	2.5 [1.1, 6.7]	3.8 [1.5, 9.2]	<0.001
LDL cholesterol, mg/dL	120.0 [99.0, 142.0]	112.0 [91.0, 135.0]	<0.001
HDL cholesterol, mg/dL	41.0 [34.0, 49.0]	36.0 [31.0, 43.0]	<0.001
Non-HDL cholesterol, mg/dL	153.0 [132.0, 179.0]	148.0 [125.0, 175.0]	<0.001
Triglycerides, mg/dL	137.0 [100.0, 199.0]	149.0 [113.0, 201.8]	<0.001
Lipoprotein(a), mg/dL	14.0 [7.0, 31.0]	17.1 [7.9, 44.0]	<0.001
Glycosylated hemoglobin (HbA1c), %	5.9 [5.5, 6.4]	6.1 [5.6, 6.7]	<0.001
Diastolic blood pressure, mmHg	81.0 [73.0, 89.0]	80.5 [73.0, 88.3]	0.402
Systolic blood pressure, mmHg	138.8 [123.3, 153.3]	141.3 [124.0, 158.7]	<0.001
Mean arterial pressure, mmHg	109.1 [98.8, 119.9]	111.3 [102.0, 121.7]	<0.001
FXI activity, %	111.0 [89.7, 138.1]	111.6 [89.0, 139.0]	0.662
NT-proBNP, ng/L	185.0 [76.0, 579.2]	349.0 [135.5, 1011.5]	<0.001
Aspirin/other antiplatelet = yes (%)	499 (48.5)	1736 (82.9)	<0.001
Vitamin K antagonis = yes (%)	87 (8.5)	116 (5.5)	0.002
CSE inhibitor (statin) = yes (%)	215 (20.9)	1259 (60.1)	<0.001
Follow-up time, years	16.8 [10.3, 17.8]	12.8 [7.3, 17.3]	<0.001

*Continuous variables are represented as median [interquartile range]. BMI, body mass index; CAD, angiography-confirmed coronary artery disease (≥50% stenosis); eGFR, estimated glomerular filtration rate (CKD-EPI cystatin C); NT-proBNP, N-terminal pro-B-type natriuretic peptide; FXI, factor XI activity (% of normal plasma).

Supplementary Table 2: NT-proBNP tertiles (ng/L), related to Figure 1 and STAR Methods.

Subset	T1 (low)	n	T2 (middle)	n	T3 (high)	n
With CAD	≤ 194.0	699	(194.0– ≤ 683.0)	698	> 683.0	698
Without CAD	≤ 102.0	343	(102.0– ≤ 367.0)	343	> 367.0	342