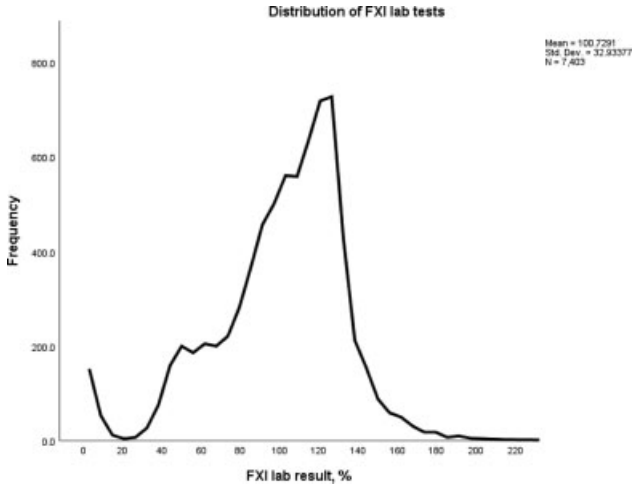
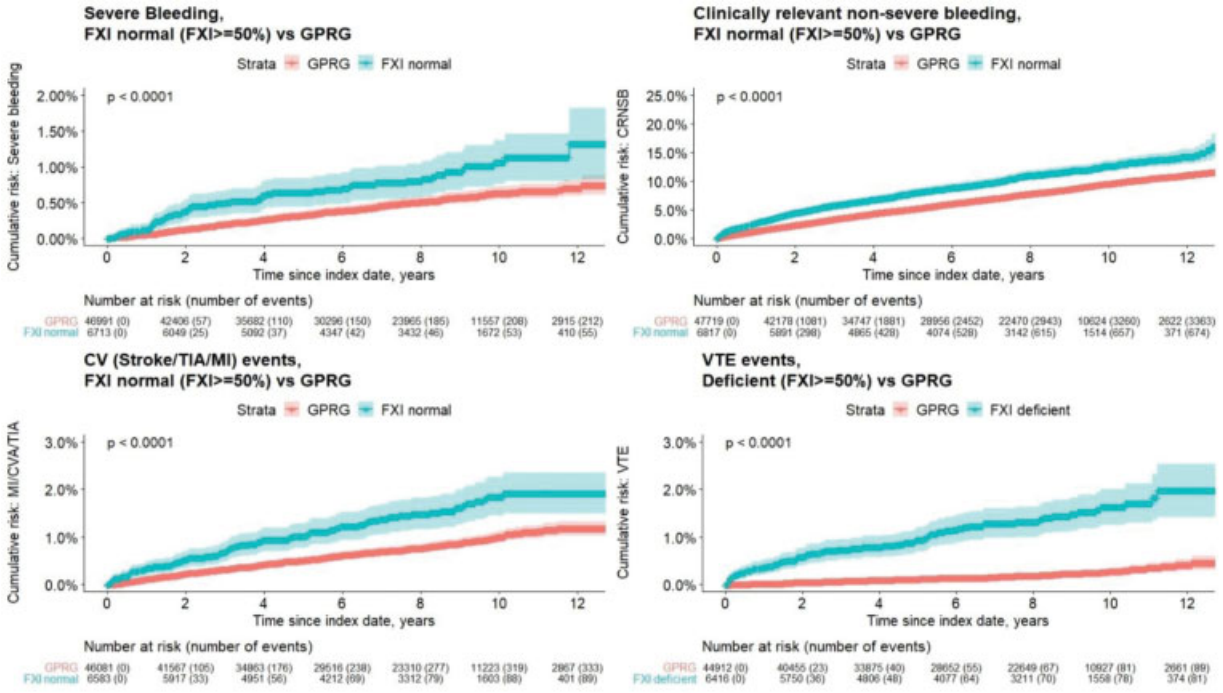
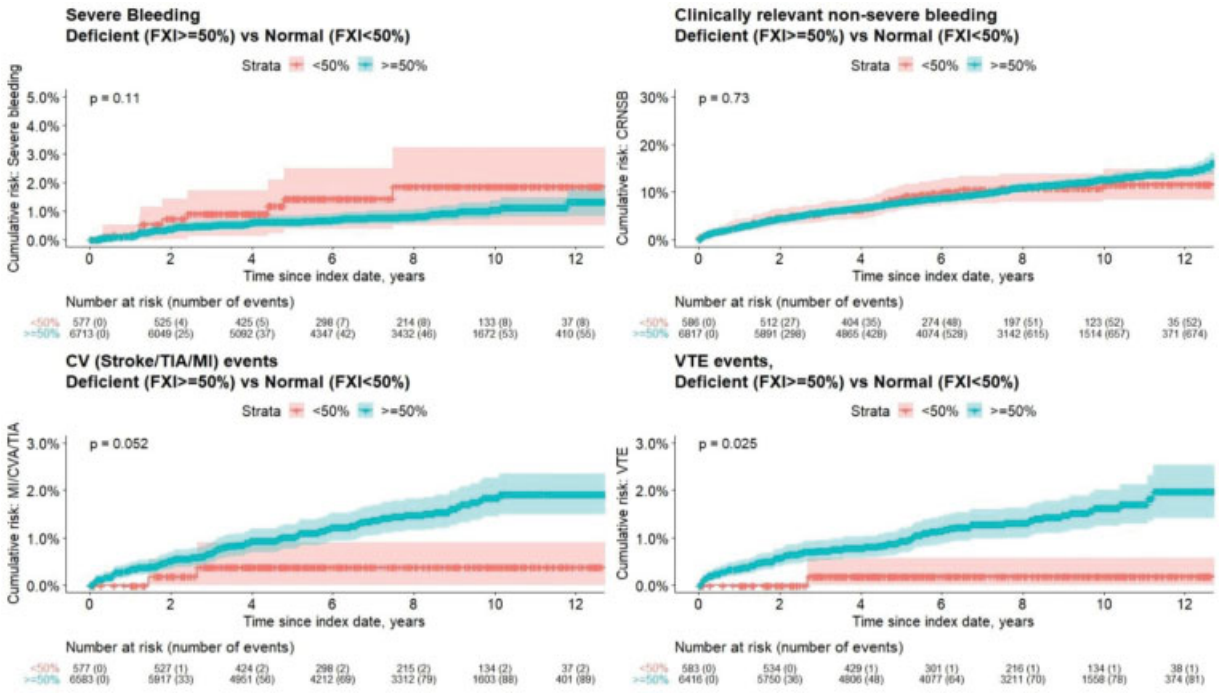


Supplementary Figure S1 Distribution of FXI activity for all patients with a FXI text, 2007–2018, $n = 7{,}403$.



Supplementary Figure S2 Cumulative incidence of severe bleeding, CRNSB, CV, and VTE events among patients with normal FXI activity levels (≥50%) compared with their matched general population reference group. CRNSB, clinically relevant nonsevere bleeding; CV, cardiovascular; FXI, factor XI; VTE, venous thromboembolism.



Supplementary Figure S3 Cumulative incidence of severe bleeding, CRNSB, CV, and VTE events among patients with FXI deficiency (<50%) and patients with normal FXI activity levels (≥ 50%). CV, cardiovascular; CRNSB, clinically relevant nonsevere bleeding; FXI, factor XI; VTE, venous thromboembolism.

Supplementary Table S1 Attrition table

	n
All patients with a FXI test result (2007–2018)	10,904
No prior cancer	10,467
≥1 year continuous eligibility in NHS	9,999
7 matches from the general population	9,823
Age ≥ 18	7,403

Supplementary Table S2 Distribution of FXI activity for each of the study cohorts

	All patients (*n* = 7,403)	No prior severe bleed (*n* = 7,290)	No prior CV event (*n* = 7,160)	No prior VTE event (*n* = 6,999)
<15%	213 (2.9%)	209 (2.9%)	208 (2.9%)	212 (3.0%)
15 to <50%	373 (5.0%)	368 (5.0%)	369 (5.2%)	371 (5.3%)
≥50%	6,817 (92.1%)	6,713 (92.1%)	6,583 (91.9%)	6,416 (91.7%)

Abbreviations: CV, cardiovascular; FXI, factor XI; VTE, venous thromboembolism.

Supplementary Table S3 10-year cumulative incidence, unadjusted, and adjusted hazard ratios comparing incident severe bleeding, CRNSB, CV, and VTE events among patients with normal FXI activity levels (≥50%) to their matched general population reference group

	N events	10-year risk (95% CI)	Unadjusted HR (95% CI)	Fully adjusted HR (95% CI)
Severe bleeding				
Factor XI cohort ≥50%, $n = 6{,}713$	55	1.10% (0.80–1.40%)	1.81 (1.34–2.43)	1.47 (1.04–2.09)
General population controls, $n = 46{,}991$	213	0.60% (0.50–0.70%)	Ref.	Ref.
Clinically relevant nonsevere bleeding				
Factor XI cohort ≥50%, $n = 6{,}817$	678	12.60% (11.70–13.60%)	1.43 (1.32–1.55)	1.28 (1.16–1.40)
General population controls, $n = 47{,}719$	3,373	9.60% (9.20–9.90%)	Ref.	Ref.
CV (stroke/TIA/MI) events				
Factor XI cohort ≥50%, $n = 6{,}583$	89	1.80% (1.40–2.30%)	1.88 (1.49–2.37)	1.73 (1.31–2.27)
General population controls, $n = 46{,}081$	333	1.00% (0.90–1.10%)	Ref.	Ref.
VTE events				
Factor XI cohort ≥50%, $n = 6{,}416$	81	1.60% (1.20–2.00%)	6.33 (4.69–8.55)	3.39 (2.36–4.86)
General population controls, $n = 44{,}912$	91	0.30% (0.20–0.30%)	Ref.	Ref.

Abbreviations: CI, confidence interval; CRNSB, Clinically relevant nonsevere bleeding; CV, cardiovascular; FXI, factor XI; HR, hazard ratio; MI, myocardial infarction; TIA, transient ischemic attack; VTE, venous thromboembolism.

Supplementary Table S4 Association between FXI deficiency and outcomes using two different reference groups

FXI activity	Analysis using normal FXI as reference group, fully adjusted HR (95% CI)	Primary analysis, fully adjusted HR (95% CI)
Severe bleeding		
< 50%, $n = 577$	1.53 (0.71–3.30)	2.56 (1.13–5.81)
Reference group	FXI activity ≥ 50%	General population
Clinically relevant nonsevere bleeding		
< 50%, $n = 586$	0.95 (0.71–1.26)	1.45 (1.08–1.97)
Reference group	FXI activity ≥ 50%	General population
Cardiovascular events		
< 50%, $n = 577$	0.28 (0.07–1.14)	0.55 (0.13–2.36)
Reference group	FXI activity ≥ 50%	General population
VTE		
< 50%, $n = 586$	0.20 (0.03–1.15)	0.45 (0.06–3.47)
Reference group	FXI activity ≥ 50%	General population

Abbreviations: CI, confidence interval; FXI, factor XI; HR, hazard ratio; VTE, venous thromboembolism.

Supplementary Table S5 Sensitivity analysis for 10-year cumulative incidence, unadjusted, and adjusted hazard ratios comparing prevalent severe bleeding among patients with FXI deficiency to their matched general population reference group

	N events	10-year risk (95% CI)	Unadjusted HR (95% CI)	Full adjusted HR (95% CI)	Full adjusted HR (95% CI), INCIDENT CASES
Severe FXI deficiency (<15%)					
Factor XI cohort, $n = 213$	1	0.50% (0.00–1.50)	0.65 (0.08–5.01)	0.60 (0.08–4.75)	0.49 (0.06–3.95)
General population controls, $n = 1,491$	11	1.30% (0.40–2.10)	Ref.	Ref.	Ref.
Partial FXI deficiency (15 to <50%)					
Factor XI cohort, $n = 373$	8	2.70% (0.80–4.70)	11.10 (3.63–33.93)	9.03 (2.92–27.97)	5.27 (1.91–14.52)
General population controls, $n = 2,611$	5	0.20% (0.00–0.50)	Ref.	Ref.	Ref.
Overall FXI deficiency (<50%)					
Factor XI cohort, $n = 586$	9	2.00% (0.60–3.40)	3.93 (1.74–8.89)	3.67 (1.61–8.36)	2.56 (1.13–5.81)
General population controls, $n = 4,102$	16	0.60% (0.30–0.90)	Ref.	Ref.	Ref.

Abbreviations: CI, confidence interval; FXI, factor XI; HR, hazard ratio.

Supplementary Table S6 Sensitivity analysis for 10-year cumulative incidence, unadjusted, and adjusted hazard ratios comparing prevalent CV events among patients with FXI deficiency to their matched general population reference group

	N events	10-year risk (95% CI)	Unadjusted HR (95% CI)	Full adjusted HR (95% CI)	Full adjusted HR (95% CI), INCIDENT CASES
Severe FXI deficiency (<15%)					
Factor XI cohort, $n = 213$	4	2.70% (0.00–5.50%)	0.89 (0.32–2.52)	1.22 (0.42–3.53)	0.55 (0.07–4.33)
General population controls, $n = 1,491$	32	3.20% (2.00–4.50%)	Ref.	Ref.	Ref.
Partial FXI deficiency (15 to <50%)					
Factor XI cohort, $n = 373$	1	0.30% (0.00–0.90%)	0.68 (0.09–5.29)	0.44 (0.05–3.47)	0.55 (0.06–4.73)
General population controls, $n = 2,611$	10	0.60% (0.20–1.00%)	Ref.	Ref.	Ref.
Overall FXI deficiency (<50%)					
Factor XI cohort, $n = 586$	5	1.10% (0.10–2.10)	0.82 (0.33–2.08)	0.85 (0.34–2.17)	0.55 (0.13–2.36)
General population controls, $n = 4,102$	42	1.50% (1.00–2.00)	Ref.	Ref.	Ref.

Abbreviations: CI, confidence interval; CV, cardiovascular; FXI, factor XI; HR, hazard ratio.

Supplementary Table S7 Sensitivity analysis for 10-year cumulative incidence, unadjusted, and adjusted hazard ratios comparing prevalent VTE events among patients with FXI deficiency to their matched general population reference group

	N events	10-year risk (95% CI)	Unadjusted HR (95% CI)	Full adjusted HR (95% CI)	Full adjusted HR (95% CI),INCIDENT CASES
Severe FXI deficiency (<15%)					
Factor XI cohort, $n = 213$	1	0.50% (0.00–1.40%)	1.02 (0.13–8.29)	0.67 (0.08–5.76)	–
General population controls, $n = 1,491$	7	0.70% (0.10–1.20%)	Ref.	Ref.	Ref.
Partial FXI deficiency (15 to <50%)					
Factor XI cohort, $n = 373$	2	0.60% (0.00–1.30%)	1.98 (0.41–9.52)	1.56 (0.32–7.56)	0.67 (0.08–5.47)
General population controls, $n = 2,611$	7	0.30% (0.10–0.60%)	Ref.	Ref.	Ref.
Overall FXI deficiency (<50%)					
Factor XI cohort, $n = 586$	3	0.50% (0.00–1.10%)	1.50 (0.43–5.21)	1.13 (0.32–3.96)	0.45 (0.06–3.47)
General population controls, $n = 4,102$	14	0.40% (0.20–0.70%)	Ref.	Ref.	Ref.

Abbreviations: CI, confidence interval; FXI, factor XI; HR, hazard ratio; VTE, venous thromboembolism.

