Coagulation factors II, V, VII, IX, X and XI and mortality: a cohort study

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BRIEF REPORT

Coagulation factors II, V, VII, IX, X and XI and mortality – a cohort study

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Abstract

Background: Elevated levels of coagulation factors (F) II (FII), FV, FVII, FIX, FX, and FXI have often been related with coronary heart disease, ischemic stroke, and venous thrombosis (VT). However, there are few studies on their associations with all-cause mortality.

Objective: We explored whether elevated levels of FII, FV, FVII, FIX, FX, and FXI are associated with an increased risk of death in patients who had VT and in individuals from the general population.

Methods: We followed 1919 patients with previous VT and 2800 age- and sex-matched community controls in whom coagulation factor levels were measured. A high coagulation factor was defined as the >90th percentile of normal in the controls. Cox regression analyses were adjusted for age and sex and for being a patient with VT or being a control subject.

Results: The median age at time of enrolment was 48 years for both patients and controls, and slightly more women than men were followed. Over a median follow-up of 6.1 years for patients and 5.0 years for controls, there were 79 and 60 deaths in patient and controls respectively. There was no association of FII, FV, FVII, FIX, FX, and FXI with all-cause mortality in patients or in control individuals.

Conclusions: Elevated levels of FII, FV, FVII, FIX, FX, and FXI levels may not be associated with an increased risk of all-cause mortality. Only for cardiac death, an association with high FX and FXI was found, which confirms the findings of previous studies, but numbers were small.

KEYWORDS
epidemiology, factor II, factor V, factor VII, factor IX, factor X, factor XI, mortality

Essentials

- High clotting factor (F) II (FII), FV, FVII, FIX, FX, and FXI are associated with heart disease, stroke, and blood clots.
- We studied whether these elevated clotting factors are associated with risk of death.
- We found that these elevated clotting factors may not be associated with death.
- However, elevated FX and FXI levels were associated with an increased risk of cardiac death.

1 | INTRODUCTION

Coagulation factors, such as fibrinogen, factor (F) VII (FVII), FVIII, and von Willebrand factor (VWF) have been associated with increased all-cause mortality [1–4]. Both the *Atherosclerosis Risk in Communities Study* and the *Multiple Environmental and Genetic Assessment of risk factors for venous thrombosis (VT) study* (MEGA study) reported that elevated levels of factor FVIII and VWF are positively associated with increased risk of mortality [1,2]. FVII has been reported to be associated with death from ischemic heart disease [3]. Similarly, FII, FV, FVII, FIX, FX, and FXI, which are involved in formation of thrombi, have been shown to be positively associated with increased risks of coronary heart disease, ischemic strokes [5,6], and VT [7] as well. Whether these coagulation factors reflect a genetic or an acquired propensity to thrombosis or surrogate markers for other vascular risk factors, or just markers for acute or chronic inflammation, or any other pathophysiological process is unclear. We hypothesized that elevated levels of FII, FV, FVII, FIX, FX, or FXI levels are associated with an increased risk of death in patients who had VT and in individuals from the general population.

2 | MATERIALS AND METHODS

We used data of patients and controls from the MEGA case-control study. Details of this study have been described previously [8]. Furthermore, 4956 consecutive patients aged 18 to 70 years with a first objectively identified deep vein thrombosis or pulmonary embolism between March 1, 1999, and August 31, 2004 were included. Controls were 3297 partners of patients and additional 3000 age- and sex-matched controls recruited via random digit dialing (RDD) between January 1, 2002, and April 1, 2005.

A detailed questionnaire was completed by each MEGA study participant on known risk factors for VT, including presence of chronic disease or malignancy in the 5 years before the index date, defined as date of diagnosis of VT for patients and partner controls. The index date for RDD controls was the date of completing the questionnaire. In patients diagnosed with VT, blood sampling for measurement of coagulation factor levels, including FII, FV, FVII, FIX, FX, and FXI, was performed before June 1, 2002. Blood samples were drawn at least 3 months after discontinuation of oral anticoagulant therapy or in patients who remained on anticoagulant therapy for >1 year. Blood sampling for partner controls was done at the same time as their partner. The RDD controls were invited for blood sampling regardless of their time of enrolment. Median time between index date and blood sampling was 10 months for patients diagnosed with VT (IQR, 8-12 months) and 6 months between index date and blood sampling for partner and RDD controls (IQR, 2-10 months).

Blood was collected in trisodium citrate and processed within 4 hours. FII, FVII, FX, and FXI activity levels were measured with a mechanical clot detection method on a STA-R coagulation analyzer. The measurements were performed following the instructions of the manufacturer (Diagnostica Stago). The levels of FIX were measured by enzyme-linked immunosorbent assay as previously described [9]. Antigenic levels of FV were determined employing a sandwich enzyme-linked immunosorbent assay as previously described [10].

Mortality data were acquired from the Dutch population registry for all MEGA participants between February 2007 and May 2009 [11]. The cause of death for deceased participants was retrieved from the national registry of death certificates. The primary outcome of this study was all-cause mortality. The observation time was from 30 days after the VT, or a similar date in the thrombosis-free cohort to either death, loss of follow-up, or end of follow-up, which was set at the date of retrieving their vital status. As it was not feasible to retrieve all mortality data at the same date, the end of follow-up was between February 2007 and May 2009.

There were 11,253 individuals in the MEGA study. Partner controls and RDDs from the general population are collectively termed as controls. For this study, we excluded participants with an active or previous history of malignancy (625 patients and 235 controls) or participants with missing data on malignancy (52 participants). We included only participants with blood samples obtained. Participants who were receiving vitamin K antagonists during the time of the blood sampling were excluded, as vitamin K antagonists lower the levels of FII, FVII, FIX, and FX. This resulted in a final cohort of 4719 individuals (1919 patients with previous VT and 2800 controls).

To investigate our hypothesis, we first determined if FII, FV, FVII, FIX, FX, and FXI were crudely associated with risk of mortality in individuals with and without VT. Continuous regression analysis for FII, FV, FVII, FIX, FX, and FXI was done. Next, percentiles (25th, 50th, 75th, and 90th) of individual factor activity levels of the control population were used as cut-off levels to compare risks of death for patients and controls in different categories of individual factor levels. We estimated incidence rates for all-cause mortality in patients with previous VT and in controls by dividing the numbers of deaths by the observation time. We evaluated risks between groups using Cox-proportional hazards models. Using levels below the 25th percentile as the reference category, hazard ratios (HRs) for death were estimated for increasing quartile levels of factor activity. We separately performed these analyses in patients with previous VT and in control subjects.

We next adjusted for age and sex. If an association remained present, we (according to our *a priori* defined protocol) next adjusted for environmental factors, comorbidities, and body mass index.

Since some of the above-mentioned coagulation factors are associated with increased risk of cardiovascular disease, we further explored whether there was an association between cardiac death, defined as death from myocardial infarction, in patients and controls by using the same strategy as defined above, with the exception that we now pooled patients and controls instead of performing a stratified analysis, in an attempt to avoid small numbers and the HRs for cardiac death were estimated using levels below the 90th percentile as the reference category. Cause-specific death analysis was adjusted for age, sex, and whether a participant was a patient or control. All statistical analyses were performed with SPSS for Windows, release 20.0 (SPSS Inc).

TABLE 1 Clinical characteristics.

	Patients with previous VT		Controls	
	Blood samples provided[a] (n = 1919)	Blood samples not provided (n = 2121)	Blood samples provided[a] (n = 2800)	Blood samples not provided (n = 3216)
Age (y)	48.3 (19-70)	47.4 (18-70)	48.0 (18-70)	45.4 (18-71)
Women	1075 (56.1%)	1154 (54.4%)	1466 (52.4%)	1743 (54.2%)
BMI (kg/m^2)	26.8 (16.5-57.8)	26.9 (15.2-63.2)	25.6 (15.7-50.3)	25.5 (15.8-50.7)
Major illness				
Diabetes	56 (2.9%)	73 (4%)	83 (3.1%)	94 (2.9%)
Liver disease	12 (0.6%)	6 (0.3%)	11 (0.4%)	11 (0.3%)
Kidney disease	13 (0.7%)	27 (1.5%)	14 (0.5%)	8 (0.2%)
Rheumatoid arthritis	48 (2.5%)	72 (4.0%)	59 (2.1%)	65 (2.0%)
Multiple sclerosis	12 (0.6%)	15 (0.8%)	9 (0.3%)	7 (0.2%)
Heart failure	19 (1.0%)	27 (1.5%)	25 (0.9%)	26 (0.8%)
Hemorrhagic stroke	13 (0.8%)	17 (0.9%)	5 (0.2%)	4 (0.1%)
Arterial thrombosis				
MI	43 (2.5%)	57 (3.1%)	51 (1.9%)	45 (1.4%)
Angina	30 (1.8%)	18 (1.0%)	25 (0.9%)	18 (0.6%)
Ischemic stroke	11 (0.6%)	19 (1.0%)	11 (0.4%)	22 (0.7%)
Transient ischaemic attack	18 (1.1%)	28 (1.5%)	22 (0.8%)	28 (0.9%)
Peripheral vascular disease	21 (1.2%)	22 (1.2%)	23 (0.9%)	23 (0.7%)
Factor II (IU/dL)	112 (22-173)		110 (16-455)	
Factor V (U/dL))	94 (40-225)		92 (34-193)	
Factor VII (IU/dL)	113 (30-250)		111 (23-219)	
Factor IX (IU/dL)	109 (61-210)		104 (42-197)	
Factor X (IU/dL)	118 (10-201)		116 (9-196)	
Factor XI (IU/dL)	105 (36-221)		100 (28-208)	
Factor VIII:C (IU/dL)	137 (38-437)		111 (3-552)	
Von Willebrand factor (IU/dL)	143 (39-715)		111 (21-825)	
Deaths (total)	79		60	
Myocardial infarction	13		4	
Stroke	0		1	
Cancer	28		26	
COPD	6		6	
Others	32		23	

Continuous variables are denoted as median (range) and categorical variables as number (%).

Data were missing for some participants in some subgroups.

BMI, body mass index, COPD, chronic obstructive pulmonary disease; MI, myocardial infarction.

[a]excludes those on warfarin at point of blood taking.

3 | RESULTS AND DISCUSSION

We included 4719 individuals consisting of 1919 patients with previous VT and 2800 controls. Table 1 shows the baseline characteristics of the 2 groups. The baseline characteristics of participants for whom a blood sample was provided compared with the total cohort were similar. Patients with VT were followed for a total of 11,487 person-years and 13,781 person-years for controls. Median follow-up was 6.1 years (IQR, 5.3-6.9 years) for patients and 5.0 years (IQR, 3.5-6.3 years) for controls. Of those who provided blood samples and

TABLE 2 Risk of death in patients with stratified levels of coagulation factors II, V, VII IX, X and XI.

	Observation years	No. of events (n)	Incidence rate, per 100 person-years (95% CI)		Hazard ratio (95% CI)	Hazard ratio[a] (95% CI)
Factor II level						
<25th percentile (<101 IU/dL)	2698.6	17	**6.3**	(3.7-10.1)	1 (reference)	1 (reference)
25th-50th percentile (102-109 IU/dL)	2114.1	11	**5.2**	(2.6-9.3)	0.8 (0.4-1.8)	1.1 (0.5-2.4)
50th-75th percentile (110-119 IU/dL)	2813.9	26	**9.2**	(6.0-13.5)	1.5 (0.8-2.7)	1.9 (1.0-3.5)
75th-90th percentile (120-128 IU/dL)	2030	15	**7.4**	(4.1-12.2)	1.1 (0.6-2.3)	1.7 (0.8-3.5)
>90th percentile (>128 IU/dL)	1301.8	6	**4.6**	(1.7-10.0)	0.7 (0.3-1.8)	1.2 (0.5-3.1)
Factor V level						
<25th percentile (<81 IU/dL)	2662.8	18	**6.8**	(4.0-10.7)	1 (reference)	1 (reference)
25th-50th percentile (81-92 IU/dL)	2854	13	**4.6**	(2.4-7.8)	0.7 (0.3-1.4)	0.5 (0.3-1.1)
50th-75th percentile (93-104 IU/dL)	2584.1	21	**8.1**	(5.0-12.4)	1.3 (0.7-2.4)	0.8 (0.4-1.5)
75th-90th percentile (105-115 IU/dL)	1686.6	13	**7.7**	(4.1-13.2)	1.1 (0.6-2.3)	0.7 (0.3-1.5)
>90th percentile (>115 IU/dL)	1392.1	14	**10.1**	(5.5-16.9)	1.6 (0.8-3.2)	0.8 (0.4-1.7)
Factor VII level						
<25th percentile (<94 IU/dL)	2623.9	12	**4.6**	(2.4-8.0)	1 (reference)	1 (reference)
25th-50th percentile (94-109 IU/dL)	2537.3	21	**8.3**	(5.1-12.7)	1.7 (0.9-3.5)	1.2 (0.6-2.4)
50th-75th percentile (110-126 IU/dL)	2995.1	18	**6.0**	(3.6-9.5)	1.2 (0.6-2.6)	0.8 (0.4-1.7)
75th-90th percentile (127-143 IU/dL)	1785.3	16	**9.0**	(5.1-14.6)	1.8 (0.8-3.8)	1.0 (0.5-2.2)
>90th percentile (>143 IU/dL)	1238	12	**9.7**	(5.0-16.9)	2.0 (0.9-4.5)	1.3 (0.6-2.9)
Factor IX level						
<25th percentile (<92 IU/dL)	2233.1	14	**6.3**	(3.4-10.5)	1 (reference)	1 (reference)
25th-50th percentile (92-103IU/dL)	2453.9	12	**4.9**	(2.5-8.5)	0.5 (0.4-1.6)	0.4 (0.2-0.8)
50th-75th percentile (104-115 IU/dL)	2620.7	17	**6.5**	(3.8-10.4)	1.0 (0.5-2.0)	0.5 (0.2-0.9)
75th-90th percentile (116-128 IU/dL)	2057.8	18	**8.7**	(5.2-13.8)	1.4 (0.7-2.7)	0.7 (0.3-1.4)
>90th percentile (>128 IU/dL)	1808.2	18	**10.0**	(5.9-15.7)	1.5 (0.7-3.0)	0.7 (0.3-1.4)
Factor X level						
<25th percentile (<104 IU/dL)	2593.4	17	**6.6**	(3.8-10.5)	1 (reference)	1 (reference)
25th-50th percentile (104-116 IU/dL)	2651.9	20	**7.5**	(4.6-11.6)	1.3 (0.7-2.5)	1.1 (0.6-2.0)
50th-75th percentile (117-129 IU/dL)	2671.5	25	**9.4**	(6.1-13.8)	1.1 (0.6-2.2)	1.3 (0.7-2.4)
75th-90th percentile (130-141 IU/dL)	1916.6	8	**4.2**	(1.8-8.2)	0.5 (0.1-1.3)	0.7 (0.3-1.7)
>90th percentile (>141 IU/dL)	1346.1	9	**6.7**	(3.1-12.7)	1.0 (0.5-2.7)	1.6 (0.7-3.6)
Factor XI level						
<25th percentile (<87 IU/dL)	2289.4	18	**7.9**	(4.7-12.4)	1 (reference)	1 (reference)
25th-50th percentile (87-98 IU/dL)	2245.4	15	**6.7**	(3.7-11.0)	0.8 (0.4-1.6)	0.9 (0.4-1.8)
50th-75th percentile (99-111 IU/dL)	2788.8	19	**6.8**	(4.1-10.6)	0.9 (0.5-1.6)	1.0 (0.5-1.9)
75th-90th percentile (112-125 IU/dL)	2083.2	13	**6.2**	(3.3-10.7)	0.8 (0.4-1.5)	0.9 (0.4-1.9)
>90th percentile (>125 IU/dL)	1772.7	14	**7.9**	(4.3-13.3)	1.0 (0.5-2.0)	1.1 (0.6-2.4)

[a]Adjusted for age and sex.

TABLE 3 Risk of death in controls with stratified levels of coagulation factors II, V, VII IX, X and XI.

	Observation years	No. of events (n)	Incidence rate, per 100 person-years (95% CI)		Hazard ratio (95% CI)	Hazard ratio[a] (95% CI)
Factor II level						
<25th percentile (<101 IU/dL)	3553.3	20	**5.6**	(3.4-8.7)	1 (reference)	1 (reference)
25th-50th percentile (102-109 IU/dL)	2869.8	12	**4.2**	(2.2-7.3)	0.8 (0.4-1.6)	0.9 (0.4-1.8)
50th-75th percentile (110-119 IU/dL)	3411.6	14	**4.1**	(2.2-6.9)	0.8 (0.4-1.5)	1.0 (0.5-1.9)
75th-90th percentile (120-128 IU/dL)	2017.5	10	**5.0**	(2.4-9.1)	0.9 (0.4-1.9)	1.2 (0.6-2.6)
>90th percentile (>128 IU/dL)	1318	4	**3.0**	(0.8-7.8)	0.6 (0.2-1.7)	0.8 (0.3-2.5)
Factor V level						
<25th percentile (<81 IU/dL)	3479.7	12	**3.4**	(1.8-6.0)	1 (reference)	1 (reference)
25th-50th percentile (81-92 IU/dL)	3493.2	11	**3.1**	(1.6-5.6)	0.9 (0.4-2.1)	0.8 (0.3-1.8)
50th-75th percentile (93-104 IU/dL)	3160.3	15	**4.7**	(2.7-7.8)	1.4 (0.7-3.0)	1.0 (0.5-2.2)
75th-90th percentile (105-115 IU/dL)	2121.5	12	**5.7**	(2.9-9.9)	1.7 (0.8-3.7)	1.0 (4.6-2.3)
>90th percentile (>115 IU/dL)	1294.8	10	**7.7**	(3.7-14.2)	2.4 (1.0-5.5)	1.5 (0.6-3.5)
Factor VII level						
<25th percentile (<94 IU/dL)	3439.9	10	**2.9**	(1.4-5.3)	1 (reference)	1 (reference)
25th-50th percentile (94-109 IU/dL)	3345.2	12	**3.6**	(1.9-6.3)	1.2 (0.5-2.9)	1.1 (0.4-2.4)
50th-75th percentile (110-126 IU/dL)	3446.1	23	**6.7**	(4.2-10.0)	2.2 (1.1-4.7)	1.7 (0.8-3.6)
75th-90th percentile (127-143 IU/dL)	1984.4	8	**4.0**	(1.7-7.9)	1.3 (0.5-3.4)	0.9 (0.4-2.3)
>90th percentile (>143 IU/dL)	1340.6	7	**5.2**	(2.1-10.8)	1.8 (0.7-4.6)	1.3 (0.5-3.5)
Factor IX level						
<25th percentile (<92 IU/dL)	3391.9	6	**1.8**	(0.6-3.9)	1 (reference)	1 (reference)
25th-50th percentile (92-103IU/dL)	3266.3	15	**4.6**	(2.6-7.6)	2.5 (1.0-6.5)	2.0 (0.8-5.1)
50th-75th percentile (104-115 IU/dL)	3328.3	14	**4.2**	(2.3-7.1)	2.3 (0.9-6.1)	1.6 (0.6-4.3)
75th-90th percentile (116-128 IU/dL)	2122.7	18	**8.5**	(5.0-13.4)	4.6 (1.8-11.5)	2.9 (1.2-7.4)
>90th percentile (>128 IU/dL)	1447.1	7	**4.8**	(1.9-10.0)	2.5 (0.9-7.6)	1.8 (0.6-5.3)
Factor X level						
<25th percentile (<104 IU/dL)	3409.7	15	**4.4**	(2.5-7.3)	1 (reference)	1 (reference)
25th-50th percentile (104-116 IU/dL)	3353.2	19	**5.7**	(3.4-8.8)	1.3 (0.7-2.5)	1.4 (0.7-2.8)
50th-75th percentile (117-129 IU/dL)	3412.5	17	**5.0**	(2.9-8.0)	1.1 (0.6-2.2)	1.3 (0.6-2.6)
75th-90th percentile (130-141 IU/dL)	2137.1	4	**1.9**	(0.5-4.8)	0.5 (0.1-1.3)	0.6 (0.2-1.7)
>90th percentile (>141 IU/dL)	1243.7	5	**4.0**	(1.3-9.4)	0.9 (0.3-2.5)	1.3 (0.5-3.5)
Factor XI level						
<25th percentile (<87 IU/dL)	3465.5	19	**5.5**	(3.3-8.6)	1 (reference)	1 (reference)
25th-50th percentile (87-98 IU/dL)	3362.3	12	**3.6**	(1.8-6.2)	0.7 (0.3-1.4)	0.7 (0.3-1.5)
50th-75th percentile (99-111 IU/dL)	3357.5	10	**3.0**	(1.4-5.5)	0.6 (0.3-1.2)	0.7 (0.3-1.4)
75th-90th percentile (112-125 IU/dL)	2133.1	10	**4.7**	(2.2-8.6)	0.8 (0.4-1.8)	0.9 (0.4-2.1)
>90th percentile (>125 IU/dL)	1237.8	9	**7.3**	(3.3-13.8)	1.3 (0.6-2.9)	1.5 (0.7-3.4)

[a]Adjusted for age and sex.

TABLE 4 Risk of cardiac death with stratified levels of coagulation factors II, V, VII, IX, X and XI.

	Observation years	No. of events (n)	Incidence rate, per 1000 person-years (95% CI)		Hazard ratio (95% CI)	Hazard ratio[a] (95% CI)
Factor II range						
≤90th percentile (≤128 IU/dL)	22568.8	14	**0.6**	(0.3-1.0)	1 (reference)	1 (reference)
>90th percentile (>128 IU/dL)	2644.6	3	**1.1**	(0.2-3.3)	1.9 (0.5-6.5)	2.4 (0.7-8.6)
Factor V range						
≤90th percentile (≤113 IU/dL)	22445.2	14	**0.6**	(0.3-1.0)	1 (reference)	1 (reference)
>90th percentile (>113 IU/dL)	2761.5	3	**1.1**	(0.2-3.2)	1.8 (0.5-6.2)	1.2 (0.3-4.1)
Factor VII range						
≤90th percentile (≤143 IU/dL)	22582.1	13	**0.6**	(0.3-1.0)	1 (reference)	1 (reference)
>90th percentile (>143 IU/dL)	2631.4	4	**1.5**	(0.4-3.9)	2.6 (0.9-8.0)	2.7 (0.9-8.8)
Factor IX range						
≤90th percentile (≤128 IU/dL)	21871.0	13	**0.6**	(0.3-1.0)	1 (reference)	1 (reference)
>90th percentile (>128 IU/dL)	3336.6	4	**1.2**	(0.3-3.1)	2.0 (0.6-6.1)	1.6 (0.5-4.9)
Factor X range						
≤90th percentile (≤141 IU/dL)	22586.5	11	**0.5**	(0.2-0.9)	1 (reference)	1 (reference)
>90th percentile (>141 IU/dL)	2627.0	6	**2.3**	(0.8-5.0)	4.7 (1.7-12.7)	6.9 (2.5-19.1)
Factor XI range						
≤90th percentile (≤125 IU/dL)	22142.2	12	**0.5**	(0.3-0.9)	1 (reference)	1 (reference)
>90th percentile (>125 IU/dL)	3071.2	5	**1.6**	(0.5-3.8)	3.0 (1.0-8.4)	2.8 (1.0-8.3)

[a]Adjusted for age, sex and case control status.

excluding those on vitamin K antagonists, there were 79 deaths in the patients and 60 deaths in the controls during follow-up.

Continuous regression analysis for FII, FV, FVII, FIX, FX, and FXI done showed no significant crude associations with any factors with all-cause mortality except FV. However, after adjustment for age and sex, the association was no longer significant.

Table 2 shows the associations in patients of FII, FVII, FIX, FX, and FXI levels expressed in 25th, 50th, 75th, and 90th percentiles with all-cause mortality. There were no associations of any factor levels with all-cause mortality.

Table 3 further shows the associations in controls of FII, FV, FVII, FIX, FX, and FXI levels, similarly expressed in 25th, 50th, 75th, and 90th percentiles with all-cause mortality in which HRs were virtually similar as the patients. There was a crude association between FV and all-cause mortality in the 90th percentile, HR = 2.4 (95% CI, 1.0-5.5). There was also a step-wise increase in risk of death for successive FV percentile levels; however, adjustment for sex and age eliminated this association, HR = 1.5 (95% CI, 0.6-3.5).

Since some of the coagulation factors we tested were reported to be associated with cardiac death, we considered a *post hoc* analysis on cardiac deaths might be of interest. For this, we pooled both cases and controls in one group and divided FII, FV, FVII, FIX, FX, and FXI into those who had a level below and above 90th percentile of individual factor levels. As shown in Table 4, there was a crude association for FX levels (HR = 4.7 [95% CI, 1.7-12.7]), which persisted after correction for age, sex, and case-control status HR = 6.9 (95% CI, 2.5-19.1). Similar results were found for high (>90th percentile) FXI levels to the risk of cardiac death and possibly also for high FII and FVII levels.

This study found that elevated coagulation factors FII, FV, FVII, FIX, FX, and FXI levels were not associated with increased all-cause mortality in both patients with previous VT and in individuals from the general population. There was a weak association in the highest percentile for FV levels in controls but when adjusted for confounders such as age and sex, the associations attenuated toward the null. Therefore, it is unlikely that a true relationship between the highest levels of FV and all-cause mortality exists. However, in a pooled analysis of patients and controls, there was a positive association between FX and FXI and cardiac death.

Thromboembolism occurs as an end result of inflammatory and/or hypercoagulable effects that disrupt the vascular endothelium and activate pro-coagulant factors, generating prothrombotic reactions [12]. The key to many prothrombotic mechanisms is an imbalance between thrombin generation and its inactivation [13]. For arterial thrombosis, such as myocardial infarction and ischemic stroke, coagulation factors such as FVII, tissue factor, FX, and FII appear to be directly linked to ischemia-reperfusion injury to the myocardium and brain [14]. FVIII is a coagulation factor that is widely associated with

increased risk of both venous and arterial thrombosis [15] and all-cause mortality [2].

Similarly, several studies have shown elevated FV, FIX, and FXI levels as a risk factor for VT [15]. The same coagulation factors, FIX and XI are associated with increased risks of coronary heart disease and ischemic stroke [1,5,6,16,17]. However, studies have been contradictory. Earlier studies showed a weak association with mortality but subsequent studies with longer follow-up and more events showed the previous associations were accounted for by classical coronary risk factors [6,18]. To our knowledge, there are no prior studies that investigated the association of FII, FV, FVII, FIX, FX, and FXI levels with all-cause mortality in individuals from a normal population and those with previous thrombosis. In this study, we have shown that there is no association between FII, FV, FVII, FIX, FX, and FXI and all-cause mortality. However, levels of FX, FXI, and potentially also FII and FVII in the >90th percentile appeared to be associated with increased risk of cardiac death. With the small number of cardiac deaths and large CIs, this result should be interpreted with caution. Furthermore, an association of FX with death or increased risks of venous or arterial thrombosis has not been reported and further studies are needed. Our study has a long follow-up of almost 6 years for patients and 5 years for controls; therefore, we could longitudinally observe if an elevated factor level could be a marker for increased risk of all-cause mortality. With this lack of association, measuring the activity level of FII, FV, FVII, FIX, or FXI would add little benefit beyond classical risk factors in predicting death.

Limitations of this study include a small number of deaths in a relatively young population; therefore, there is a risk of type II error especially in the high percentile groups (ie, >90th percentile of normal coagulation factor levels). Coagulation factors were only measured once and may not be definitively predictive of mortality. Our study cohort consists mainly of a Dutch, Caucasian population and studies have shown that FIX and FXI differ in age and ethnicity, with Caucasians having lower factor levels than African-Americans [19]. Therefore, our results may not be applicable to all ethnic and age groups.

In conclusion, elevated FII, FV, FVII, FIX, FX, and FXI levels may not be associated with an increased risk of all-cause mortality in a young population. Further studies in an older population would be useful.

AUTHOR CONTRIBUTIONS

E.S.Y. performed the statistical analyses, interpreted the data and wrote the manuscript; F.R.R. and S.C.C. interpreted the data and reviewed the manuscript; F.R.R. was responsible for the MEGA study; W.M.L. designed the analyses and reviewed the manuscript.

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RELATIONSHIP DISCLOSURES

There are no competing interests to disclose.

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