Paper I

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ORIGINAL ARTICLE

Impact of incident myocardial infarction on the risk of venous thromboembolism: the Tromsø Study

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Essentials

- Registry-based studies indicate a link between arterial- and venous thromboembolism (VTE).
- We studied this association in a cohort with confounder information and validated outcomes.
- Myocardial infarction (MI) was associated with a 4.8-fold increased short-term risk of VTE.
- MI was associated with a transient increased risk of VTE, and pulmonary embolism in particular.

Summary. *Background:* Recent studies have demonstrated an association between venous thromboembolism (VTE) and arterial thrombotic diseases. *Objectives:* To study the association between incident myocardial infarction (MI) and VTE in a prospective population-based cohort. *Methods:* Study participants (n = 29 506) were recruited from three surveys of the Tromsø Study (conducted in 1994–1995, 2001–2002, and 2007–2008) and followed up to 2010. All incident MI and VTE events during follow-up were recorded. Cox regression models with age as the time scale and MI as a time-dependent variable were used to calculate hazard ratios (HRs) of VTE adjusted for sex, body mass index, blood pressure, diabetes mellitus, HDL cholesterol, smoking, physical activity, and education level. *Results:* During a median follow-up of 15.7 years, 1853 participants experienced an MI and 699 experienced a VTE. MI was associated with a 51% increased risk of VTE (HR 1.51; 95% confidence interval [CI] 1.08–2.10) and a 72% increased risk of pulmonary embolism (PE) (HR 1.72; 95% CI 1.07–2.75), but not significantly associated with the risk of deep vein thrombosis (DVT) (HR 1.36; 95% CI 0.86–2.15). The highest risk estimates for PE were observed during the first 6 months after the MI (HR 8.49; 95% CI 4.00–18.77). MI explained 6.2% of the PEs in the population (population attributable risk) and 78.5% of the PE risk in MI patients (attributable risk). *Conclusions:* Our findings indicate that MI is associated with a transient increased VTE risk, independently of traditional atherosclerotic risk factors. The risk estimates were particularly high for PE.

Keywords: epidemiology; myocardial infarction; pulmonary embolism; risk factors; venous thromboembolism.

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Introduction

Despite definite differences in pathology and treatment strategies, growing evidence suggests a bidirectional relationship between venous thromboembolism (VTE) (deep vein thrombosis [DVT] and pulmonary embolism [PE]) and arterial thromboembolic diseases (ATDs) (myocardial infarction [MI] and ischemic stroke) [1–4]. The relationship between ATD and VTE could be attributable to shared risk factors, such as obesity, smoking, or a family history of MI, indirect causal factors, such as hospitalizations accompanied by periods of immobilization, or a direct causal relationship, such as a transient prothrombotic response secondary to sudden tissue damage, and venous stasis following heart failure [5].

The results from prospective cohorts, applying cause-specific regression models, have revealed that, among the traditional atherosclerotic risk factors, only age, obesity

and a familial predisposition for MI are shared risk factors for ATD and VTE [6–9]. In a case–control study, patients with unprovoked VTE were reported to have a higher frequency of carotid plaques than control participants [2]. Conversely, subsequent large population-based cohort studies have failed to confirm an association between carotid atherosclerosis and VTE [10–12], indicating that atherosclerosis is not a shared risk factor for ATD and VTE.

Population-based registry studies have shown that patients with a history of MI are at increased short-term risk of subsequent VTE [13,14]. However, results from registry-based linkage studies should be interpreted with caution, as they often lack information about confounders and have limited validation of exposure and outcomes. For instance, an evaluation of the Danish National Patient Registry revealed that the positive predictive values for VTE diagnoses from emergency departments and hospitals were only 44% and 67–77%, respectively [15]. Moreover, the lack of important clinical information, such as body mass index (BMI), has limited our ability to adjust for confounding in previous registry-based studies [13,14].

We therefore aimed to investigate the association between MI and the future risk of VTE in a population-based cohort with validated information on exposure (MI), the endpoint (VTE), and potential confounders.

Materials and methods

Study population

The Tromsø Study is a single-center, prospective, population-based study, with repeated health surveys of the inhabitants of Tromsø, Norway. Study participants were recruited from the fourth, fifth and sixth surveys of the Tromsø Study, conducted in 1994–1995, 2001–2002, and 2007–2008, respectively. The overall attendance rates were high: 77% in the fourth survey, 78% in the fifth survey, and 66% in the sixth survey. A detailed description of the Tromsø Study has been published elsewhere [16]. In total, 30 586 unique participants aged 25–97 years participated in at least one of the surveys, and, of these, 21 529 participants participated in two or all three surveys. Participants who did not consent to medical research (n = 225), participants not officially registered as inhabitants of the municipality of Tromsø at the date of study enrollment (n = 48) and participants with a previous history of VTE (n = 78) or MI (n = 729) before baseline were excluded. Consequently, 29 506 participants were included in the study, and followed from the date of enrollment to the end of follow-up, i.e. 31 December 2010 (Fig. 1). The regional committee for medical and health research ethics in North Norway approved the study, and all participants gave their informed written consent.

Baseline measurements

Information about study participants was collected by physical examination, from blood samples and from self-administrated questionnaires at each survey. Systolic and diastolic blood pressures were measured three times at 1-min intervals with an automatic device (Dinamap Vital Signs Monitor, 1846; Critikon, Tampa, FL, USA), with the participant in a sitting position after 2 min of rest, and defined as the mean of the last two readings. Non-fasting blood samples were collected from an antecubital vein; serum was prepared by centrifugation with 3000 × g in 10 min after 1 hour in open air at room temperature, and analyzed at the Department of Clinical Chemistry, University Hospital of North Norway (UNN), Tromsø, Norway. Serum total cholesterol was analyzed by use of an enzymatic colorimetric method with a commercially available kit (CHOD-PAP; Boehringer-Mannheim, Mannheim, Germany). Serum HDL cholesterol was measured after the precipitation of lower-density lipoproteins with heparin and manganese chloride. Height and weight were measured with participants wearing light clothes and no shoes. BMI was calculated as weight in kilograms divided by the square of height in meters (kg m^{-2}). Obesity (BMI of ≥ 30 kg m^{-2}) was classified according to the World Health Organization (WHO) definition [17]. Hypertension was classified as a mean systolic blood pressure of ≥ 140 mmHg, a mean diastolic blood

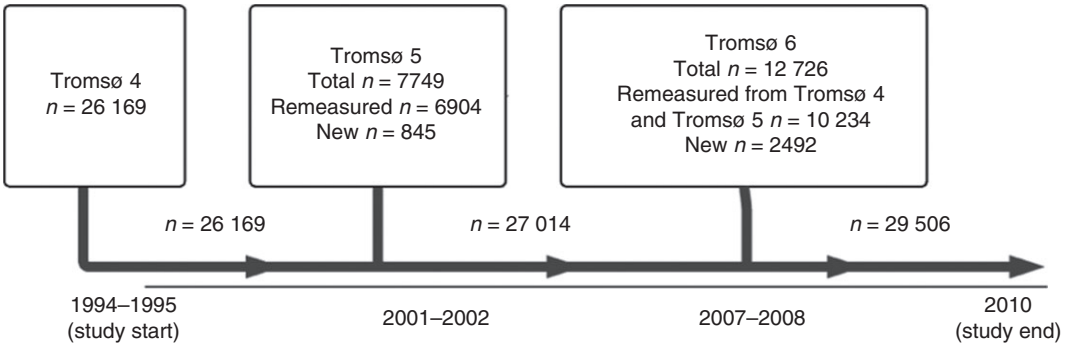

Fig. 1. Inclusion of study participants from the fourth (1994–1995), fifth (2001–2002) and sixth (2007–2008) surveys of the Tromso Study.

pressure of ≥ 90 mmHg, or self-reported use of blood pressure-lowering drugs. Hypercholesterolemia was classified as a total serum cholesterol level of ≥ 6.5 mmol L^{-1} or self-reported use of lipid-lowering drugs. Information on family history of MI, diabetes mellitus, physical activity and education level was collected from a self-administered questionnaire.

Assessment of MI

Adjudication of hospitalized and out-of-hospital MI events was performed by an independent endpoint committee, and based on data from hospital and out-of-hospital medical records, autopsy records, and death certificates. The national 11-digit identification number allowed linkage to national and local diagnosis registries. Cases of incident MI were identified by linkage to the hospital discharge diagnosis registry at the UNN, by searching for ICD-9 codes 410-414 and 430-438 in the time period 1994–1998, and thereafter ICD-10 codes I20-I25 and I60-I69. The hospital medical records were retrieved for case validation. Modified WHO MONICA/MORGAM criteria for MI [18] were used, and included clinical symptoms and signs, findings in electrocardiograms, values of cardiac biomarkers, and autopsy reports when applicable. Furthermore, linkage to the National Causes of Death Registry at Statistics Norway allowed the identification of fatal incident MI cases that occurred as out-of-hospital deaths, including deaths that occurred outside of Tromsø. The death certificates were used to collect relevant information on the MI events from additional sources, such as autopsy reports and records from nursing homes, ambulance services, and general practitioners.

Registry of VTE

All incident VTE events during follow-up were identified by searching the hospital discharge diagnosis registry, the autopsy registry and the radiology procedure registry at the UNN, as previously described [19]. The UNN is the only hospital in the region, and all diagnostic radiology and hospital care is provided exclusively by this hospital. The medical record for each potential VTE case was reviewed by trained personnel, and a VTE event was considered to be verified and recorded when the presence of clinical signs and symptoms of DVT or PE were combined with objective confirmatory tests (i.e. compression ultrasonography, venography, spiral computed tomography, perfusion–ventilation scan, pulmonary angiography, or autopsy), and resulted in a VTE diagnosis that required treatment, as previously described in detail [19]. VTE cases from the autopsy registry were recorded when the death certificate indicated VTE as the cause of death or as a significant condition associated with death. The VTE events were classified as provoked or unprovoked according to the presence of provoking factors at the time of diagnosis. Provoking factors included recent surgery or trauma within the previous 8 weeks, acute medical conditions (i.e. acute MI, ischemic stroke, or major infectious diseases), active cancer, immobilization (i.e. bed rest for > 3 days, wheelchair use, or long-distance travel exceeding 4 h within the 14 days prior to the event), or any other factor described by a physician in the medical record (e.g. intravascular catheter).

Statistical analysis

Participants who developed MI during the study period contributed with non-exposed person-time from the inclusion date to the date of a diagnosis of MI, and then with exposed person-time from the date of MI onwards. For each participant, non-exposed and exposed person-years were counted from the date of enrollment to the date of an incident diagnosis of VTE or to the date on which the participant died or moved from Tromsø, or until the end of the study period, i.e. 31 December 2010, whichever came first. Participants who died or moved from the municipality during follow-up were censored at the date of death or migration.

Statistical analyses were performed with STATA version 14.0 (Stata Corporation, College Station, TX, USA). Crude incidence rates (IRs) of VTE were calculated, and expressed as number of events per 1000 person-years at risk. Cox proportional hazards regression models were used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs) of VTE, DVT and PE after MI. Age was used as the time scale in the Cox model, with the age of the participants at study enrollment being defined as entry time, and the age at the time of the VTE event or censoring event (i.e. death, migration, or the date of study end) being defined as exit time. MI was included as a time-dependent covariate in the Cox model. Therefore, participants who developed MI during follow-up contributed with person-years in both the unexposed and exposed group. For those who participated in several surveys, information on possible potential confounders was updated at each survey. We estimated HRs with three different models. The first model was adjusted for age (as time scale) and sex, and the second model was additionally adjusted for BMI. The third model was adjusted for age (as time scale), sex, BMI, diabetes mellitus, smoking, systolic blood pressure, HDL cholesterol, physical activity, and education.

The proportional hazards assumption was tested by the use of Schoenfeld residuals, and found to be not violated. Statistical interactions between MI and sex were tested by including cross-product terms in the proportional hazards models, and no interactions were found.

Attributable risk (AR), i.e. the proportion of events among the exposed participants that could be explained by the exposure, was calculated from IRs of VTE in the MI (I_e) and non-

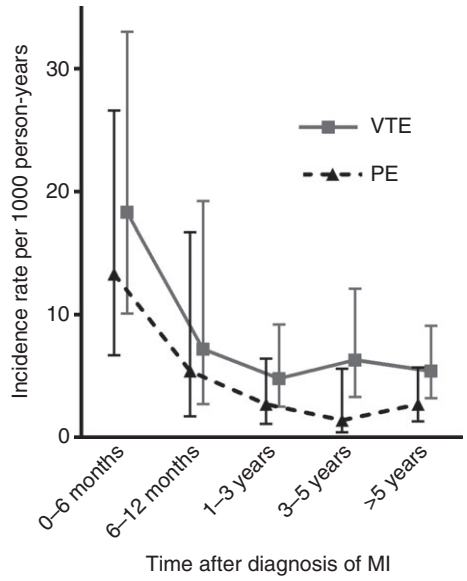

Fig. 2. Changes in crude incidence rates per 1000 person-years for venous thromboembolism (VTE) and pulmonary embolism (PE) in the periods 0–6 months, 6–12 months, 1–3 years, 3–5 years and more than 5 years after myocardial infarction (MI).

MI (I_o) populations, and expressed as a percentage (AR = 100 × [I_e – I_o]/I_e). Population AR (PAR), i.e. the proportion of events in the population that could be attributed to the exposure, was calculated on the basis of IRs of VTE in the total population (I_p) and in the non-exposed population (I_o), and expressed as a percentage (PAR = 100 × [I_p – I_o]/I_p). GRAPHPAD PRISM version 6.0 (GraphPad Software, San Diego, CA, USA) was used to generate a figure showing the change in VTE risk over time (Fig. 2).

Results

There were 1892 (6.4%) participants who developed a first-time MI, and 699 (2.4%) participants who developed a first-time VTE, during a median of 15.7 years of follow-up. The baseline characteristics of the study participants with and without MI are shown in Table 1. Participants with MI had a higher mean age and a higher BMI, and included a higher proportion of men, smokers and participants with hypertension than those without MI (Table 1).

The characteristics of the VTE events are shown in Table 2. Among the 699 VTE events, 405 (57.9%) were DVTs and 294 (42.1%) were PEs. Moreover, 358 events (51.2%) were classified as provoked, and 341 events (48.8%) were classified as unprovoked. The most frequent provoking factors were active cancer, immobilization, and surgery (Table 2). The proportion of PEs was higher among the VTE events that occurred after an MI (53% versus 41%) than among the VTE events that appeared in the absence of a previous MI. Furthermore, surgery was a more frequent provoking factor for VTE in participants with prior MI (27%) than in those without MI (15%) (data not shown).

Table 1 Baseline characteristics of participants without and with myocardial infarction (MI) (n = 29506); the Tromsø Study 1994–2010

	No MI (n = 27614)	MI (n = 1892)
Age (years), mean ± SD	45 ± 14	62 ± 13
Sex (male), % (n)	45.9 (12675)	61.0 (1154)
BMI (kg m^{-2}), mean ± SD	25.2 ± 3.9	26.6 ± 4.1
Total cholesterol (mmol L^{-1}), mean ± SD	5.90 ± 1.27	6.92 ± 1.28
HDL (mmol L^{-1}), mean ± SD	1.50 ± 0.41	1.41 ± 0.40
Triglycerides (mmol L^{-1}), mean ± SD	1.51 ± 1.02	1.95 ± 1.18
Systolic blood pressure (mmHg), mean ± SD	132 ± 19	152 ± 24
Diastolic blood pressure (mmHg), mean ± SD	77 ± 12	87 ± 14
Hypertension*, % (n)	31.5 (8700)	70.7 (1337)
Hypercholesterolemia†, % (n)	30.5 (8429)	63.0 (1192)
Smoking‡, % (n)	35.6 (9803)	41.2 (780)
Physical activity§, % (n)	33.4 (9210)	20.0 (380)
Education¶, % (n)	34.1 (9406)	12.2 (231)
Self-reported diabetes mellitus, % (n)	1.5 (401)	6.3 (120)

BMI, body mass index; SD, standard deviation. *Mean systolic/diastolic blood pressure of ≥ 140/≥ 90 mmHg, use of antihypertensives, or self-reported hypertension. †Total cholesterol level of ≥ 6.5 mmol L−1, use of lipid-lowering drugs, or self-reported hypercholesterolemia. ‡Self-reported daily smoking; yes/no. §One or more hours of moderate or hard physical activity per week; yes/no. ¶More than 10 years of education.

Table 2 Characteristics of venous thromboembolism events (n = 699); the Tromsø Study 1994–2010

	% (n)
Clinical characteristics	
Deep vein thrombosis	57.9 (405)
Pulmonary embolism	42.1 (294)
Provoked	51.2 (358)
Unprovoked	48.8 (341)
Clinical risk factors	
Oestrogen*,†	5.9 (41)
Pregnancy/puerperium*	0.9 (6)
Heredity‡	3.4 (24)
Provoking factors	
Surgery	15.5 (108)
Trauma	7.9 (55)
Cancer	24.0 (168)
Immobility§	18.3 (128)
Other¶	4.9 (34)

*Only women were included in the analysis. †Current or previous use of hormone replacement therapy or oral contraceptives. ‡Myocardial infarction in a first-degree relative before age 60 years. §Bed rest for > 3 days, journeys of > 4 h by car, boat, train or air within the last 14 days, or other types of immobilization. ¶Other provoking factor described by a physician in the medical record (e.g. intravascular catheter).

IRs and HRs of VTE and subtypes of VTE according to MI are shown in Table 3. In participants without MI, 652 VTE events were identified during 354 865

person-years of follow-up (IR of 1.8 per 1000 person-years), whereas there were 47 VTE events during 7062 person-years of follow-up in participants exposed to MI (IR of 6.7 per 1000 person-years). Overall, participants with a previous MI had a 51% (HR 1.51; 95% CI 1.09–2.11) higher VTE risk than participants without a previous MI in a multivariable model adjusted for traditional atherosclerotic risk factors, including sex, BMI, systolic blood pressure, diabetes mellitus, HDL cholesterol, smoking, physical activity, and education level (Table 3). In a subgroup of participants with available data on family history of MI ($n = 21\ 096$), the addition of a family history of MI to the multivariable model did not change the risk estimates for the association between MI and VTE (Table S1). In separate analyses of PE and DVT after MI, PE showed higher risk estimates than DVT. The multivariable HRs were 1.72 (95% CI 1.07–2.79) for PE and 1.36 (95% CI 0.86–2.15) for DVT (Table 3).

In analyses stratified by the presence of provoking factors, MI was associated with increased risks of provoked VTE (multivariable adjusted HR 1.83; 95% CI 1.21–2.79) and provoked PE (multivariable adjusted HR 2.29; 95% CI 1.20–4.37), but not with provoked DVT or any unprovoked events (Table 4). Among MI patients, 72.4% of the VTEs could be attributed to the MI (AR), and 4.7% of the VTE events in the entire study population could be attributed to the MI (PAR). For PE, the numbers attributable to MI were higher; the AR was 78.5%, and the PAR was 6.2%.

IRs and HRs of VTE were high immediately after the MI, and declined rapidly thereafter (Table 5; Fig. 2). The IR of VTE was 18 per 1000 person-years, and the HR of VTE was five-fold higher in participants with MI than in

Table 3 Incidence rates (IRs) and hazard ratios (HRs) of venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE) according to myocardial infarction (MI) exposure; the Tromsø Study 1994–2010

	Person-years	VTE events	Crude IR (95% CI)*	Model 1†, HR (95% CI)	Model 2‡, HR (95% CI)	Model 3§, HR (95% CI)
Total VTE						
No MI	354 865	652	1.8 (1.7–2.0)	Reference	Reference	Reference
MI	7062	47	6.7 (5.0–8.9)	1.49 (1.10–2.01)	1.41 (1.04–1.92)	1.51 (1.09–2.11)
DVT						
No MI	354 865	383	1.1 (1.0–1.2)	Reference	Reference	Reference
MI	7062	22	3.1 (2.1–4.7)	1.25 (0.81–1.93)	1.17 (0.75–1.83)	1.36 (0.86–2.15)
PE						
No MI	354 865	269	0.8 (0.7–0.9)	Reference	Reference	Reference
MI	7062	25	3.5 (2.4–5.2)	1.80 (1.18–2.73)	1.71 (1.12–2.60)	1.72 (1.07–2.79)

CI, confidence interval. *Per 1000 person-years. †Model 1: age as time scale, adjusted for sex. ‡Model 2: model 1 + body mass index. §Model 3: model 2 + systolic blood pressure, diabetes mellitus, HDL cholesterol, smoking, physical activity, and education level.

Table 4 Incidence rates (IRs) and hazard ratios (HRs) for venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE) according to myocardial infarction (MI) exposure by the presence of predisposing factors; the Tromsø Study 1994–2010

	Person-years	VTE events	Crude IR (95% CI)*	Model 1†, HR (95% CI)	Model 2‡, HR (95% CI)	Model 3§, HR (95% CI)
Provoked VTE						
No MI	354 865	331	0.9 (0.8–1.0)	Reference	Reference	Reference
MI	7062	27	3.8 (2.6–5.6)	1.65 (1.11–2.46)	1.63 (1.09–2.42)	1.83 (1.21–2.79)
Unprovoked VTE						
No MI	354 865	321	0.9 (0.8–1.0)	Reference	Reference	Reference
MI	7062	20	2.8 (1.8–4.4)	1.32 (0.83–2.09)	1.19 (0.75–1.91)	1.16 (0.67–2.00)
Provoked DVT						
No MI	354 865	216	0.6 (0.5–0.7)	Reference	Reference	Reference
MI	7062	15	2.1 (1.3–3.5)	1.44 (0.85–2.47)	1.45 (0.85–2.48)	1.59 (0.91–2.76)
Unprovoked DVT						
No MI	354 865	167	0.5 (0.4–0.5)	Reference	Reference	Reference
MI	7062	7	1.0 (0.5–2.1)	0.96 (0.44–2.07)	0.79 (0.35–1.80)	1.02 (0.45–2.34)
Provoked PE						
No MI	354 865	115	0.3 (0.3–0.4)	Reference	Reference	Reference
MI	7062	12	1.7 (1.0–3.0)	2.00 (1.09–3.67)	1.91 (1.04–3.50)	2.29 (1.20–4.37)
Unprovoked PE						
No MI	354 865	154	0.4 (0.4–0.5)	Reference	Reference	Reference
MI	7062	13	1.8 (1.1–3.2)	1.65 (0.92–2.94)	1.56 (0.88–2.79)	1.29 (0.62–2.67)

CI, confidence interval. *Per 1000 person-years. †Model 1: age as time scale, adjusted for sex. ‡Model 2: model 1 + body mass index. §Model 3: model 2 + systolic blood pressure, diabetes mellitus, HDL cholesterol, smoking, physical activity, and education level.

Table 5 Incidence rates (IRs) and hazard ratios (HRs) for venous thromboembolism (VTE), deep vein thrombosis (DVT) and pulmonary embolism (PE) according to time after myocardial infarction (MI); the Tromsø Study 1994–2010

	Person-years	VTE events	Crude IR (95% CI)*	Model 1†, HR (95% CI)	Model 2‡, HR (95% CI)	Model 3§, HR (95% CI)
VTE						
No MI	354 865	652	1.8 (1.7–2.0)	Reference	Reference	Reference
< 6 months	601	11	18.3 (10.1–33.0)	4.38 (2.41–7.98)	4.26 (2.34–7.75)	4.82 (2.57–9.05)
0.5–1 year	556	4	7.2 (2.7–19.2)	1.72 (0.64–4.61)	1.68 (0.63–4.49)	2.10 (0.78–5.62)
1–3 years	1880	9	4.8 (2.5–9.2)	1.14 (0.59–2.20)	1.10 (0.57–2.13)	1.20 (0.60–2.42)
3–5 years	1428	9	6.3 (3.3–12.1)	1.45 (0.75–2.81)	1.40 (0.72–2.71)	1.56 (0.77–3.14)
>5 years	2598	14	5.4 (3.2–9.1)	1.11 (0.65–1.89)	1.00 (0.58–1.74)	0.90 (0.46–1.74)
DVT						
No MI	354 865	383	1.1 (1.0–1.2)	Reference	Reference	Reference
< 6 months	601	3	5.0 (1.6–15.5)	2.08 (0.67–6.52)	2.05 (0.66–6.42)	2.41 (0.77–7.54)
0.5–1 year	556	1	1.8 (0.3–12.8)	0.76 (0.11–5.43)	0.75 (0.11–5.37)	0.89 (0.13–6.38)
1–3 years	1880	4	2.1 (0.8–5.7)	0.89 (0.33–2.39)	0.88 (0.33–2.36)	1.03 (0.38–2.77)
3–5 years	1428	7	4.9 (2.3–10.3)	2.04 (0.96–4.32)	1.99 (0.94–4.23)	1.14 (1.14–5.15)
> 5 years	2598	7	2.7 (1.3–5.7)	1.00 (0.47–2.13)	0.85 (0.38–1.90)	0.89 (0.37–2.16)
PE						
No MI	354 865	269	0.8 (0.7–0.9)	Reference	Reference	Reference
< 6 months	601	8	13.3 (6.7–26.6)	7.46 (3.67–15.17)	7.13 (3.51–14.48)	8.49 (4.00–18.17)
0.5–1 year	556	3	5.4 (1.7–16.7)	2.98 (0.95–9.32)	2.83 (0.90–8.85)	3.78 (1.20–11.89)
1–3 years	1880	5	2.7 (1.1–6.4)	1.46 (0.60–3.54)	1.38 (0.57–3.35)	1.45 (0.53–3.91)
3–5 years	1428	2	1.4 (0.4–5.6)	0.72 (0.18–2.92)	0.68 (0.17–2.76)	0.44 (0.06–3.18)
> 5 years	2598	7	2.7 (1.3–5.7)	1.24 (0.58–2.64)	1.18 (0.56–2.52)	0.90 (0.33–2.45)

CI, confidence interval. *Per 1000 person-years. †Model 1: age as time scale, adjusted for sex. ‡Model 2: model 1 + body mass index. §Model 3: model 2 + systolic blood pressure, diabetes mellitus, HDL cholesterol, smoking, physical activity, and education level.

those without MI during the first 6 months after the incident MI diagnosis (adjusted HR 4.86; 95% CI 2.57–9.05). Following the initial 6 months after the MI, the VTE risk was not significantly increased (Table 5). Separate analysis of PE showed a similar, although augmented, risk pattern. The multivariable HR for PE during the first 6 months after MI was 8.49 (95% CI 4.00–18.17). The PE risk remained almost four-fold higher from 6 months to 1 year after the MI than the risk in those without MI (adjusted HR 3.78; 95% CI 1.20–11.89), but the association disappeared when the observation period was extended beyond 1 year (Table 5).

Discussion

In our population-based cohort, participants with MI had a higher risk of subsequent VTE, and PE in particular, than participants without MI in analyses adjusted for traditional atherosclerotic risk factors. The risk estimates for PE were highest during the first 6 months after the MI, and declined rapidly thereafter. We found that 78.5% of the PE events among MI patients could be attributed to the MI, whereas 6.2% of the PEs in the population could be attributed to MI.

Previous studies have indicated an association between MI and an increased risk of future VTE. In a meta-analysis of placebo-controlled trials evaluating the effect of antithrombotic drugs, 4% of patients with MI had a symptomatic PE during the first 2 weeks after the MI event [20]. A relationship between MI and PE was further supported by a cross-sectional study, in which an association between coronary heart disease and PE was found in patients aged ≥ 60 years [21]. In agreement with our findings, Sørensen *et al*. found that the risk of VTE, and of PE in particular, was higher in the first months immediately after an MI than the VTE risk in population-based controls in two registry-based case–control studies [13,14].

The explanations for the observed association between MI and the future VTE risk are not yet known. Potential mechanisms include shared risk factors, indirect factors, or a direct causal relationship [5]. If the association between MI and VTE is attributable to shared cardiovascular risk factors, the cardiovascular risk factors work as confounding factors by increasing the risks of both MI and VTE. In agreement with this, cohort studies conducting cause-specific analyses have revealed age, obesity and a family history of MI as shared risk factors for MI and VTE [6–9]. Conversely, our findings argue against a strong impact of shared risk factors on the association between MI and the future VTE risk. First, shared risk factors would mediate a permanent and not a transient VTE risk, as observed in our study. Second, adjustments for atherosclerotic risk factors, such as obesity and a family history of MI, would substantially attenuate the association between MI and subsequent VTE if the risk factors were actual confounders. In our study, adjustments for atherosclerotic risk factors had a marginal impact on the risk estimates for the association between

MI and VTE. However, our findings do not exclude the possibility of joint effects between shared inherited prothrombotic risk factors that would augment the VTE risk under circumstances of high thrombosis risk related to the MI itself (e.g. hospitalizations accompanied by periods of immobilization, a transient prothrombotic response secondary to sudden tissue damage, and venous stasis following heart failure) [22,23]. Furthermore, several other risk factors for VTE, including high levels of coagulation factors VIII, IX, and XI, plasminogen activator inhibitor-1, and von Willebrand factor, have also been shown to be risk factors for arterial cardiovascular disease [24,25]; the levels of these increase immediately after MI, and may therefore mediate the transient VTE risk after MI observed in our study.

The transient increase in the VTE risk after MI points towards causal mechanisms related to the MI itself. Patients with MI are hospitalized and temporarily immobilized, both of which are strong predisposing factors for VTE [26]. Previous studies have suggested that hospitalization after MI partly explains the observed association between MI and subsequent VTE [13,27]. This suggestion was supported by the short-term nature of the risk [13] and the attenuation of risk estimates after adjustment for hospitalization for surgery or acute medical illness, as well as nursing home confinement [27]. Accordingly, we observed a transient short-term VTE risk after MI, and stratified analyses revealed higher risk estimates for provoked than for unprovoked events. In agreement with previous observations [13,14,27], our findings support the notion that indirect causal factors, such as hospitalization and subsequent immobilization, as well as coronary artery bypass surgery or endovascular procedures after MI, may contribute substantially to the observed association between MI and VTE.

A direct causal relationship between MI and VTE may also contribute to the VTE risk in MI patients. Local disturbances in the cardiopulmonary circulation after MI may predispose to thrombus formation by stasis in the pulmonary circulation, owing to backward failure secondary to left ventricular dysfunction [28,29], by injury to the vascular endothelium [30], or by activation of the coagulation system during the acute phase of MI [31]. Atrial fibrillation is a frequent complication after MI [32]. Recently, we reported that atrial fibrillation was associated with an increased risk of VTE, and of PE in particular [33]. According to the transient nature of the VTE risk and the particularly high PE risk observed in our study, it is likely that direct causal mechanism(s) secondary to local disturbances in the cardiopulmonary circulation or electromechanical activity (e.g. atrial fibrillation) may be responsible for some of the VTE risk after MI. Previous studies have shown that DVT can be identified in only 50% of patients with PE [34], which supports the concept that pulmonary thrombi may form *de novo* in the lungs or originate from other sources of emboli. Alternatively, the high PE rather than DVT risk after MI may be explained by detection bias, as patients with previous MI are more likely to undergo examinations for chest pain.

Our findings may have some clinical implications. In our population-based cohort, 6.2% of PE events could be attributed to MI exposure, and 78% of the VTE events among the MI patients were attributable to the MI itself. These numbers may actually be underestimates, owing to the concomitant use of drugs (aspirin, heparins, and statins) in MI, which is known to reduce the VTE risk. The high amount of PE explained by exposure to MI may suggest that anticoagulant treatment of MI patients would prevent several subsequent PE events. Randomized clinical trials have shown that prolonged oral anticoagulant treatment with vitamin K antagonists (VKAs) is equal to (Waris II trial) [35] or superior to (ASPECT II trial) [36] antiplatelet treatment for recurrent MI. Unfortunately, none of these studies has reported VTE as a secondary endpoint. Furthermore, VKAs and non-vitamin K oral anticoagulants (NOACs) have been shown to reduce the incidence of recurrent VTE by ~ 90%. However, the impact of anticoagulant treatment together with antiplatelet treatment for prevention of PE in MI patients needs to be weighed against the expected bleeding risk resulting from combined treatment [35,37–39]. Alternatively, the transient nature of the VTE risk after MI suggests that MI patients may benefit more from extended thromboprophylaxis with low molecular weight heparins or NOACs, with an expected efficacy of 50–70% prevention of VTEs over the first 3–6 months [40,41].

Major strengths of our study include the prospective design, the large number of participants recruited from a general population, the long-term follow-up, the wide age distribution, the updated confounder information, and the validated VTE and MI events. As many cardiovascular risk factors are modifiable, some participants' individual risk profiles may change during follow-up, leading to regression dilution bias and an underestimation of the associations. However, an advantage of our study is the repeated measurements of participant characteristics during follow-up. Because of this, we can explore the real effect of cardiovascular risk factors on the outcomes during follow-up to a greater extent, resulting in more reliable risk estimates than in a traditional cohort study. However, our study has some potential limitations. In a cohort study, non-response bias is a possible limitation. Those who participate in cohort studies tend to be healthier and more interested in their health than the general population. Our estimated incidence may therefore be lower than the true incidence. Furthermore, the low numbers of both exposure and outcome events in the present cohort may lead to low statistical power for assessing the potential impact of MI on the VTE risk, particularly in subgroup analyses.

In conclusion, the present cohort study implies that first-lifetime MI is associated with an increased risk of

VTE, and particularly of PE. The transient nature of the VTE risk after MI suggests that direct or indirect causal mechanisms related to the MI event itself are primarily responsible for the observed association. We found that 6.2% of the VTE events in the population could be attributed to MI.

Addendum

L. B. Rinde was responsible for data analysis and writing of the manuscript. C. Lind was responsible for data interpretation and revision of the manuscript. B. Småbrekke was responsible for data interpretation and revision of the manuscript. I. Njølstad was responsible for data collection and revision of the manuscript. E. B. Mathiesen was responsible for data collection and revision of the manuscript. T. Wilsgaard was responsible for statistical support and revision of the manuscript. M.-L. Løchen was responsible for data collection and revision of the manuscript. E. M. Hald was responsible for data collection and interpretation, and revision of the manuscript. A. Vik was responsible for data interpretation and revision of the manuscript. S. K. Brækkan was responsible for conception and design of the study, data collection and interpretation, and writing of the manuscript. J.-B. Hansen was responsible for conception and design of the study, data collection and interpretation, and writing of the manuscript.

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Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Incidence rates and hazard ratios for VTE, DVT and PE after acute MI, including only subjects with data on family history (n = 21 096).

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Supplemental Tables

Supplementary Table I for Online Data Supplement. Incidence Rates and Hazard Ratios for VTE, DVT and PE after AMI including only subject with data on family history (n=21 096)

	Person-years	VTE-events	Crude IR (95% CI)*	HR (95% CI)†	HR (95% CI)†!‡	HR (95% CI)†!‡
Total VTE						
No AMI	279152	472	1.7 (1.5-1.9)	Reference	Reference	Reference
AMI	5381	30	5.6 (3.9-8.0)	1.24 (0.85-1.81)	1.26 (0.83-1.92)	1.25 (0.82-1.90)
DVT						
No AMI	279152	277	1.0 (0.9-1.1)	Reference	Reference	Reference
AMI	5381	12	2.2 (1.3-3.9)	0.90 (0.50-1.62)	1.01 (0.55-1.86)	0.99 (0.54-1.83)
PE						
No AMI	279152	195	0.7 (0.6-0.8)	Reference	Reference	Reference
AMI	5381	18	3.5 (2.1-5.3)	1.66 (1.02-2.72)	1.60 (0.90-2.86)	1.59 (0.89-2.84)

AMI indicates acute myocardial infarction; CI, confidence interval; DVT, deep vein thrombosis; HR, hazard ratio; IR, incidence rate; PE, pulmonary embolism; and VTE, venous thromboembolism.

*Per 1000 persons-years

†Adjusted for age (as time scale) and sex-adjusted

!Adjusted for body mass index

‡Adjusted for systolic blood pressure, diabetes mellitus, HDL, smoking, physical activity, education level, and family history of myocardial infarction.