Myocardial Infarction as a Transient Risk Factor for Incident Venous Thromboembolism: Results from a Population-based Case-Crossover Study

Running head: Role of myocardial infarction as a transient risk factor for venous thrombosis

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Abstract

Patients with myocardial infarction (MI) are at increased short-term risk of venous thromboembolism (VTE). The mechanisms behind this association are unclear. We aimed to investigate the impact of acute MI as a transient risk factor for incident VTE while taking other concomitant VTE risk factors into account. We conducted a case-crossover study of VTE patients (n=707) recruited from the fourth survey of the Tromsø study. VTE risk factors and hospitalizations were registered during the 90-day period preceding the VTE diagnosis (hazard period) and in four 90-day control periods. Conditional logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs) for VTE according to acute MI and after adjustment for other risk factors. Additionally, we applied a mediation analysis to quantify how much the known transient risk factors account for the observed effect of MI on VTE risk. MI was recorded in 13 (1.8%) of the hazard periods and in 6 (0.2%) of the control periods, which yielded a crude OR of 11.9 (95% CI: 3.9-36.7). Adjustment for immobilization and infection yielded an OR of 2.7 (95% CI: 0.6-11.2). The OR was attenuated to 2.6 (95% CI: 0.6-11.9) after further adjustment for major surgery, trauma, red blood cell transfusion and central venous catheterization. Approximately 60% of the association between MI and VTE was mediated through infection and immobilization. In conclusion, our findings suggest that the increased VTE risk after MI may to a large extent be explained by concomitant conditions related to MI, particularly infections and immobilization.

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), is a prevalent and potentially fatal cardiovascular disease (1). VTE has been acknowledged as the third leading cause of cardiovascular-associated deaths in Western countries, after myocardial infarction (MI) and ischemic stroke (2, 3).

During the last decade, several population-based studies have reported that MI patients are at increased risk of subsequent VTE (4-6), especially during the first months after the MI. In a large cohort, we recently showed that the short-term risk of VTE after MI was particularly pronounced for provoked VTE and PE (6). The pathophysiological mechanisms behind the increased risk of VTE after MI are still unclear. Among potentially shared risk factors, only advancing age and obesity have been consistently associated with both MI and VTE (2, 7, 8). The short-term increase in VTE risk suggests that mechanisms related to the MI itself (a direct causal effect) or indirect mechanisms due to hospitalization after MI may play a role (9). Heart failure with subsequent left ventricular ejection fraction (LVEF) reduction and ultimately venous stasis in the cardiopulmonary circulation could be a direct biomechanical mechanism related to the MI that increases VTE risk (10). Moreover, in the short time span after the MI, a substantial prothrombotic state with an increase in both concentration and activity of circulating coagulation factors has been reported (11-14). Thus, MI itself can potentially serve as a trigger for VTE. On the other hand, the short-term risk of provoked VTE after MI (6) implies that indirect mechanisms may be important contributors to the increased VTE risk. Concomitant presence of transient risk factors for VTE (e.g. infections, immobilization, major surgery, central venous catheter etc.) following an MI could result in a short period with particularly high thrombosis risk (15).

To what extent an MI serves as a direct trigger for VTE has not been extensively investigated. The aim of the present study was therefore to investigate the role of MI as a transient risk factor for VTE after accounting for other concomitant VTE risk factors in a case-crossover study. A case-crossover design is well-suited for studying transient risk factors, because each case serves as his or her own control, and persistent confounders are therefore largely controlled for by the design.

Materials and methods

Study population

The study population was recruited from the fourth survey of the Tromsø Study (conducted in 1994/1995), which is a single-center, population-based cohort with repeated health surveys of the inhabitants of the municipality of Tromsø, Norway. The Tromsø Study is described in detail elsewhere (16). To the fourth survey all inhabitants aged ≥25 years were invited, and 77% of the eligible population participated. All first lifetime VTE events during follow-up in the study population were recorded from the date of enrollment in 1994/95 until December 31, 2012. The VTE cases were identified by thorough review of hospital and out-patient clinic records, as previously described in detail (17). A VTE event was adjudicated when clinical signs and symptoms of DVT or PE were combined with an objectively confirmatory radiological procedure (e.g. compression ultrasonography, venography, CT, perfusion-ventilation scan, pulmonary angiography, or autopsy), and resulted in a VTE diagnosis that required treatment (e.g. anticoagulant treatment with low-molecular-weight heparin, vitamin K-antagonists or similar agent, thrombolytics or vascular surgery).

Study design

We used a case-crossover design including all the incident cases of VTE (n=707) occurring among the participants of the fourth survey of the Tromsø Study during the period 1994-2012. In this design, each participant serves as his/hers own control, and characteristics that do not vary within an individual (e.g. history of comorbid conditions, chronic conditions, health behaviors, anthropometric measures and inherited thrombophilias) are controlled for through the study design (18). The risk period of interest was the 90-day period before the date of VTE (hazard period), and exposures during this 90-day period were compared with exposures during four preceding 90-day periods (control periods). The length of these hazard and control periods was pre-defined based on the definition of provoking factors, as described by Kearon et al (19). A wash-out period of 90 days was implemented between the hazard period and control periods in order to avoid carry-over effects (18, 20) (Figure 1). For each VTE case, trained personnel searched the hospital records for relevant transient risk factors, diagnostic procedures, surgical and medical treatment, laboratory tests and diagnosis during hospital admission and outpatient clinic visits in any of the hazard or control periods. We did not have access to medical records from general practice.

Definition of a transient risk factor

Transient risk factors were recorded if they were present in the 90-day hazard period or in any of the 90-day control periods. MI was defined as the presence of an acute MI diagnosis in the medical record. The diagnosis of MI was based on a combination of clinical signs and symptoms together with electrocardiography findings and measurements of cardiac enzymes in blood samples. Immobilization was defined as the presence of one or more of the following characteristics: bedrest for three days or more, ECOG (Eastern Cooperative Oncology Group) score of four, or other immobilizing factors specified in the patient's medical record (e.g.

confinement to wheelchair, cast immobilization, etc.). Infection was recorded if an acute

infection was noted by a physician in the patient's medical record. The definition included

both community-acquired infections that required hospital admission and hospital-acquired

infections (21). Major surgery, trauma, red blood cell transfusion and use of central venous

catheter were recorded if described in the medical record. If an exposure occurred over

several days, it was considered to have occurred if any of the days of the exposure fell within

the specified 90-day period.

Statistical analysis

Statistical analyses were performed using STATA version 15.0 (Stata Corporation, College

Station, TX USA). Conditional logistic regression was used to calculate odds ratios (ORs)

with 95% confidence intervals (CIs) for VTE according to acute MI and after adjustment for

other transient risk factors. In Model 1, we calculated the crude OR for the association

between MI and VTE. In model 2, we adjusted for immobilization and infection since these

variables are potential transient risk factors for VTE that often co-exist with MI. In model 3,

we additionally adjusted for other transient VTE risk factors including major surgery, trauma,

red blood cell transfusion and central venous catheterization (multivariable analysis) by

entering them simultaneously and one-by-one in the regression model (22). In addition to the

overall analyses, subgroup analyses were performed for DVT and PE. We also conducted a

sensitivity analysis where those with a diagnosis of active cancer (n=176) in the hazard period

were excluded.

Immobilization and infection can be consequences of MI, and could therefore mediate

the association between MI and VTE (23). We applied the method developed by Karlson,

Holm and Breen (KHB-method) to investigate whether and to what extent immobilization and

infection mediate the relationship between MI and VTE (24-26). The technical details and

mathematical proofs of the KHB-method are available elsewhere (25). In brief, this method estimates all (e.g., direct, indirect and total) effects on the same scale, and the coefficients in the conditional logistic regression models are not affected by rescaling, particularly when the total effect is decomposed into the direct and indirect effects (27). This property allows us to compare the coefficients without any scale identification issues. Additionally, the KHB-method has the important feature that it can handle more than one mediator simultaneously and it can decompose the contribution from the different mediators while adjusting for other factors. The link function *clogit* (conditional logistic regression) was applied with the hazard- or control period as outcome, MI as main exposure, infection and immobilization as mediators and major surgery, trauma, red blood cell transfusion and central venous catheter as additional covariates.

Results

Characteristics of the study participants are presented in Table 1. Among the 707 VTE cases, there were 408 DVTs (57.7%) and 299 PEs (42.3%) with or without concomitant DVT. The median age at VTE diagnosis was 71 years and 53.6% were women.

The distribution of transient risk factors for VTE in the hazard and control periods is shown in Table 2. Among the 707 patients, 13 (1.8%) had a diagnosis of MI in the hazard period and 6 (0.2%) in a control period. Immobilization occurred in 222 (31.4%) of the hazard periods and in 57 (2.0%) of the control periods. Acute infection occurred in 267 (37.8%) of the hazard periods and in 107 (3.8%) of the control periods.

Table 3 shows the frequencies of MI in the hazard and control periods, and the corresponding ORs for VTE, DVT and PE. The estimated risk of VTE was high for MI, with a crude OR of 11.9 (95% CI: 3.9-36.7). The OR for VTE associated with MI decreased to 2.7

(95% CI: 0.6-11.2) after adjustment for immobilization and infection in Model 2. When these variables were entered into the model one by one, the OR for VTE associated with MI adjusted for immobilization was 8.1 (95% CI: 2.2-30.2) whereas adjustment for infection yielded an OR of 3.9 (95% CI: 1.0-14.7). Adding the other VTE risk factors (i.e. major surgery, trauma, red blood cell transfusion and central venous catheter) in a third model along with immobilization and infection, only marginally attenuated the OR (OR 2.6, 95% CI: 0.6-11.9) (Table 3, Model 3).

In subgroup analyses on risk of DVT and PE according to MI status, the results were virtually the same as those observed for overall VTE (Table 3). In the crude models, the ORs were 14.9 (95% CI: 3.1-70.4) for DVT and 8.9 (95% CI: 0.6-19.6) for PE, respectively. As for the overall analyses the associations were substantially attenuated after adjustment for all VTE risk factors (Model 3), and the ORs were 2.9 (95% CI: 0.6-19.6) and 1.8 (95% CI: 0.1-26.9) for DVT and PE, respectively. In the sensitivity analysis, where cases with active cancer in the hazard period were excluded (n=176), the ORs did not differ markedly from those of the main analyses (Supplementary table 1).

Furthermore, we analyzed the potential magnitude of the mediating effect of immobilization and infection on the relationship between MI and VTE. Table 4 presents the mediation analysis adjusted for major surgery, trauma, red blood cell transfusion and central venous catheterization. Approximately 60% of the association between MI and VTE was mediated through immobilization and infection (Table 4), of which 72% was attributed to infection and 28% to immobilization (Figure 2).

Discussion

In the present case-crossover study comprising VTE patients recruited from a general population, we aimed to assess the impact of acute MI as a transient risk factor for incident VTE. We found that MI was associated with a substantially increased risk of VTE. However, the association between MI and VTE was largely attenuated when adjusting for potential mediators. The mediation analysis revealed that 60% of the total effect of MI on VTE risk was attributed to concomitant infection- and/or immobilization. Our findings suggest that the increased short-term risk of VTE associated with MI to a large extent can be explained by the presence of other conditions related to the MI, particularly infection and immobilization.

Despite the fact that several studies have confirmed an association between incident MI and risk of venous thrombosis, the mechanisms for this association are uncertain. To our knowledge, no previous study has investigated this relationship using a case-crossover design. With this design, we confirmed that MI was a transient risk factor for VTE within the first three months, but that the main drivers of this increased short-term VTE risk were concurrent infection and immobilization. Our findings are in line with a case-control study from Olmsted County, which reported that the strength of the association between MI and VTE was attenuated after adjustment for all other factors associated with VTE in univariate analyses (28).

Infection can be both a risk factor for MI (29) and a complication following an MI (30), and thus could act as both a confounder and a mediator for VTE risk. Unfortunately, the temporal sequence between MI and infection could not be determined in our study. Nevertheless, our adjustment and mediation analyses indicated that concomitant infection (regardless of whether it was a cause or a consequence of the MI) was an important contributor to increased VTE risk in patients with MI. A meta-regression analysis based on 36 studies of risk factors for MI reported that 0.6% (31) of the MIs in the population was

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attributed to respiratory infections. Serious infections occur in 2-3% of MI patients treated with primary percutaneous coronary intervention (PCI) and are associated with an adverse 90-day outcome and prolonged hospital stay (32). The rate of serious infections after coronary artery bypass graft (CABG) surgery ranges from 0.3-4.0% (33). Although the overall rate of infections in MI patients appears to be low, infection may still play an important role in VTE-risk stratification of MI patients. The potential discriminatory power of infection on VTE risk should therefore be investigated in a prospective study of MI patients.

Immobilization is another recognized risk factor for VTE (34) and appear to be an important mediator of VTE risk in MI patients. Infection and immobilization often co-exist (21, 35), and the combined exposure has been reported to yield a synergistic effect on VTE risk (21). Current guidelines recommend use of thromboprophylaxis with low molecular weight heparin (LMWH), low-dose unfractionated heparin or fondaparinux for hospitalized acutely ill medical patients throughout the period of immobilization or acute hospital stay (36, 37). However, since patients with MI are frequently treated with dual antiplatelet therapy in the initial phase after coronary intervention (38, 39), their risk of bleeding is additionally increased. A risk assessment model that discriminates MI patients at high and low risk of VTE is therefore particularly needed to achieve a favorable benefit-to-harm ratio for thromboprophylaxis (40-42). Our findings suggest that both infection and immobilization should be considered in the development of new risk prediction models for VTE in MI patients.

Even though the risk of VTE in patients with MI was largely explained by other risk factors, MI was still associated with an increased risk of VTE after adjustment for all the other well-established risk factors for VTE with an OR of 2.6. Potentially, this remaining risk could be ascribed to pathophysiological mechanisms related to the MI itself. Heart failure with subsequent left ventricular ejection fraction reduction and ultimately stasis in the

cardiopulmonary circulation is common after MI (10). Moreover, a prothrombotic state in the early phases after an MI (43-45), as well as a persistent coagulation activation long after clinical stabilization (13), has been reported.

Surgery is a strong risk factor for VTE (23). However, further adjustment for surgery did not affect the risk estimates in our study, implying that endovascular procedures or CABG after MI may not contribute to the risk of VTE in the absence of infection and immobilization.

Strengths of our study include the case-crossover design with unselected VTE patients, which enabled us to focus on transient risk factors while controlling for potential persistent confounders such as inherited thrombophilias, chronic conditions and anthropometric measures. Our study has some limitations. Even if fixed confounders are controlled for through the study design, the presence of residual confounding cannot be ruled out as other unmeasured or unknown transient risk factors could have influenced the association between MI and VTE. In addition, we cannot rule out that comorbidities related to risk of both MI and VTE has developed during the 1.5 year follow-up. Furthermore, surveillance bias might have occurred, as physicians could be more aware of VTE risk factors when VTE is suspected than during admission for other conditions in the control periods. If so, this would lead to an overestimation of the impact of such risk factors on the risk of VTE (21), potentially resulting in an over-adjustment of the association between MI and VTE. The temporal sequence between MI and exposure to the other risk factors could not fully be determined, and unfortunately, we could not distinguish whether immobilization and infection acted as confounders or mediators of the association between MI and VTE. Hence, a prospective cohort of MI patients is warranted to study the temporal sequence between exposure, intermediates and outcome. Information on MI-exposure was based on review of medical records with no further outcome validation. However, exposure misclassification is unlikely due to the fact that a diagnosis of MI is based on a combination of objective criteria from

electrocardiography findings and measurements of cardiac enzymes in blood samples together with clinical signs and symptoms (46). Lastly, due to the small sample size and some wide confidence intervals, our estimates must be interpreted with caution.

In conclusion, our findings suggest that the increased short-term risk of VTE after MI to a large extent may be explained by concomitant conditions related to the MI, particularly infections and immobilization.

Authors' contribution

J.K. Sejrup contributed to statistical analysis, data interpretation, and drafted the manuscript. T. Børvik, G. Grimnes and T. Isaksen contributed to data collection, data interpretation, and revision of the manuscript. K. Hindberg contributed to statistical analysis, data interpretation, and revision of the manuscript. J.B Hansen and V.M. Morelli contributed to the conception and design of the study, data interpretation, and revision of the manuscript. S.K Brækkan contributed to the conception and design of the study, data collection, statistical analysis, data interpretation, and revision of the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflict of interest

None.

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Table 1 Characteristics of the study participants

	At time of VTE diagnosis (n=707)
Median age (years±SD)	71 ± 14
Female sex (n, %)	379 (53.6)
Deep vein thrombosis (n, %)	408 (57.7)
Pulmonary embolism* (n, %)	299 (42.3)

Values are absolute numbers (n) with percentages of total hazard/control periods

*Pulmonary embolism with or without concomitant deep vein thrombosis

Table 2 The distribution of transient risk factors for VTE in the hazard and control periods

Transient risk factors	Hazard period (n=707)	Control periods (n=2828)
MI (Myocardial infarction) (n, %)	13 (1.8)	6 (0.2)
Immobilization (n, %) †	222 (31.4)	57 (2.0)
Infection (n, %)	267 (37.8)	107 (3.8)
Major surgery (n, %)	118 (16.7)	88 (3.1)
Red blood cell transfusion (n, %)	82 (11.6)	28 (1.0)
Trauma (e.g. fracture) (n, %)	71 (10.0)	25 (0.9)
Central venous catheter (n, %)	56 (7.9)	17 (0.6)

Values are absolute numbers (n) with percentages of total hazard/control periods

† Bedrest>3 days, ECOG 4, other immobilizing factor specifically recorded

Table 3 Distribution of MI in the hazard and control periods and odds ratios (ORs) of venous thromboembolism, deep vein thrombosis and pulmonary embolism

	Hazard period n (%)	Control periods n (%)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
VTE	**n=707[a]**	**n=2828**			
MI	13 (1.8)	6 (0.2)	11.9 (3.9-36.7)	2.7 (0.6-11.2)	2.6 (0.6-11.9)
DVT	**n=408[b]**	**n=1632**			
MI	8 (2.0)	3 (0.2)	14.9 (3.1-70.4)	3.3 (0.6-19.6)	2.9 (0.5-17.8)
PE	**n=299[b]**	**n=1196**			
MI	5 (1.7)	3 (0.3)	8.9 (1.7-46.7)	2.0 (0.2-22.5)	1.8 (0.1-26.9)

CI, confidence interval; OR, odds ratio

The reference category was "no MI"

[a]707 venous thrombosis cases, four control periods for each case

[b]408 deep vein thrombosis-cases, four control periods for each case; 299 pulmonary embolism cases, four control periods for each case

Model 1: Unadjusted odd ratio

Model 2: Adjusted for infection and immobilization

Model 3: Adjusted as in Model 2 with addition of major surgery, trauma, red blood cell transfusion and central venous catheter

Table 4 The KHB mediation analysis (24, 25) and decomposition results for the association between MI and VTE

Conditional logistic regression			
	Coefficient	SE	Mediation percentage
Coefficients			
Total effect	2.43	0.77	-
Direct effect	0.96	0.77	-
Mediating effect	1.47*	0.71	60.5
Through			
Infection	1.06	0.28	71.8
Immobilization	0.42	0.35	28.2

*p<0.005