

Risk Factors for Venous Thromboembolism in Medical Patients: Data from the GEMINI and MASTER Registries

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INTRODUCTION

Hospitalized patients with acute medical conditions are at significant risk of venous thromboembolism (VTE): approximately 10-30% of general medical patients may develop deep vein thrombosis or pulmonary embolism, and the latter is a leading contributor to deaths in hospital [1]. Medical conditions considered associated with a moderate to high risk of VTE include cardiac, respiratory and infectious diseases, and cancer [2]. Estimates of the level of risk of VTE in medical inpatients are essentially based on the findings of clinical trials on VTE prophylaxis. However, the patient population enrolled in these trials is not necessarily representative of the general medical setting, due to selection criteria, and it may only partially reflect the complexity of medical patients, frequently characterized by advanced age, comorbidities, and additional, patient-specific multiple risk factors [3, 4].

Data from large, real-world registries may provide useful information, to integrate those arising from clinical trials, in order to evaluate the impact of potential risk factors for VTE. In this report we analyze the results of two surveys (GEMINI and MASTER) recently performed in Italy.

MATERIALS AND METHODS

GEMINI was a prospective observational study including 4846 unselected medical patients enrolled in 27 Italian Departments of Internal Medicine, whose primary aim was to assess the frequency of clinically overt VTE (both diagnosed at admission or "hospital-acquired") [5]. Further objectives of the study were to evaluate the clinical impact of potential risk factors for VTE, and the attitude of physicians towards antithrombotic prophylaxis in this patient population.

The MASTER Registry was a multicenter study recruiting 2119 consecutive VTE patients in 25 primary or secondary thrombosis centers. Aim of the registry was to prospectively collect data on the epidemiology and long-term clinical outcome of VTE from a large unselected cohort of patients, including an analysis of risk factors, diagnostic and therapeutic procedures [6].

RESULTS

In the context of GEMINI, a multivariable analysis has been performed to evaluate the association between some potential risk factors and the occurrence of VTE in the study population. As specified in Table 1, previous VTE and bed resting were significantly associated with the risk of VTE, while a trend for increased risk was documented in cancer patients, in the case of recent surgery, and for obesity. Chronic heart failure and obstructive pulmonary disease appeared inversely related to occurrence of VTE, while a very low number or no VTE events occurred in patients with myocardial infarction and inflammatory bowel disease, so determining extremely wide confidence intervals for odds ratios.

Table 1. Potential Risk Factors and Association with Venous Thromboembolism in the GEMINI Study

Variable	Effect	OR	95% CI
Age	> 75 vs ≤ 75	0.96	0.62 - 1.49
Previous VTE	Yes vs No	8.52	4.14 - 17.53
Recent surgery	Yes vs No	1.45	0.28 - 7.48
Obesity	Yes vs No	1.19	0.71 - 2.00
CHF	Yes vs No	0.15	0.05 - 0.48
Acute MI	Yes vs No	< 0.001	< 0.001 - > 999.9
COPD exacerbation	Yes vs No	0.43	0.20 - 0.91
IBD	Yes vs No	< 0.001	< 0.001 - > 999.9
Cancer	Yes vs No	1.45	0.88 - 2.38
Hemi-paraparesis /plegia	Yes vs No	0.69	0.28 - 1.66
Fever	Yes vs No	0.69	0.38 - 1.25
Bed rest *	Yes vs No	2.99	1.91 - 4.71

* Chronic bedridden patients, or bed resting > 3 days in the four weeks prior to study inclusion, or > 3 days during hospital stay - VTE = venous thromboembolism; CHF = congestive heart failure; MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; IBD = inflammatory bowel disease.

A specific attention was devoted, by the Authors of the MASTER Registry, to the subgroup of cancer patients. According to data from MASTER, the clinical presentation of acute VTE is different and often more extensive in cancer patients than in patients free from malignancy, and cancer affects management of VTE making it more problematic [7].

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The incidence of VTE has been described as increasing exponentially with age [8, 9]. In the MASTER registry elderly patients (more than 75 years of age) were more likely to have pulmonary embolism at presentation (33.6% vs 25.6%, $p < 0,001$), and in this subgroup the risk of VTE was significantly associated with immobilization (odds ratio 2.46, 95% confidence interval 1.85-3.27) and with severe medical disorders (odds ratio 1.99, 95% confidence interval 1.41-2.80) [10].

COMMENTS

Observational studies may provide interesting scientific data since they are generally representative of real-life, however, due to potential confounding factors, these data need attention and caution, particularly when they conflict with current knowledge.

In the recent GEMINI survey, previous VTE and bed rest are confirmed as strong risk factors for venous thromboembolism in medical patients, in spite of a broad use of prophylaxis when these conditions were present. In our opinion this fact requires a specific attention and possibly a more aggressive prophylactic strategy in these patients, than actually done.

No association with a greater risk of VTE was evident in GEMINI in patients aged more than 75 years, or in the case of congestive heart failure, or chronic obstructive pulmonary disease. These results seem not coherent with current knowledge [11], and they deserve possible explanations. As a first evaluation, in GEMINI elderly patients, patients with congestive heart failure, or chronic obstructive pulmonary disease, received antithrombotic prophylaxis at a quite large extent, therefore reasonably reducing the risk of VTE. Further, age has been previously reported as independent risk factor for VTE in hospitalized medical patients [12]; however, in a recent observational study, age > 75 years was not significantly related to an increased risk [13]. As far as patients with congestive heart failure or respiratory disease are concerned, recommendation to use prophylaxis in this setting mainly relies on the results of trials of thromboprophylaxis selecting patients with disease at high level of severity [14-16]. The study population of GEMINI was more heterogeneous as for severity of the diseases and, since the majority of VTE events in this survey occurred in outpatients, it is reasonable that heart failure and pulmonary obstructive disease were at that time at a low level of activity, if any.

Available data from literature document that cancer patients are at increased risk for VTE, and active cancer accounts for around 20% of all new VTE events occurring in the community [2]. Results from GEMINI study seem to support the concept that cancer may be related to a higher risk of VTE, though this association did not reach statistical significance. This trend, together with findings from the MASTER registry showing that VTE in cancer is often more extensive and difficult to manage, seems to us worth noting and claims a more precise definition of risk profile in the heterogeneous category of cancer patients.

As a general issue, in real-life hospitalized medical patients constitute a complex population with advanced mean age, often multiple comorbidities, and frequent conditions (i.e. obesity, renal failure) in which optimal prophylaxis for VTE is not defined. To identify criteria for a reliable and easy-to-use risk assessment, though a difficult goal to achieve due to peculiarities and complexity of medical patients, could lead to a more systematic and probably broader use of antithrombotic prophylaxis in this setting, potentially leading to a further reduction of the burden of VTE.

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