A new era for venous thromboembolism prevention in medical inpatients

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Historically, hospital-related venous thromboembolism (VTE) has been thought to mainly occur in surgical patients (1). Several phase III randomised controlled trials (RCTs) have investigated benefits and harms of pharmacologic thromboprophylaxis in this setting (1). Subsequently, acutely ill hospitalised medical patients have been recognised to be at increased risk of VTE, with approximately 75% of all VTE-related deaths diagnosed in autopsy studies occurring in non-surgical patients (2). Based on such compelling evidence, a number of RCTs have been carried out which consistently shown the clinical benefit of pharmacologic thromboprophylaxis also in medical inpatients (3, 4). Conversely, 3 phase III RCTs, i.e. EXCLAIM, ADAPT, and MAGELLAN studies, have subsequently failed to support the extended use of thromboprophylaxis beyond the first two weeks of treatment in this setting due to an excess in bleeding rates (5-7). The results of these trials have raised again concerns on the true clinical benefit of anticoagulant prophylaxis in a population that is mainly represented by fragile, elderly patients (8). The widespread existence of these concerns is confirmed by the fact that despite high-quality evidence supporting in-hospital prophylaxis and recommendations from international guidelines, thromboprophylaxis in acutely ill medical inpatients remains substantially underused (9-11).

Appropriate patient selection remains a major issue and a number of pitfalls in proposed strategies have been identified. First, the group-specific thromboembolic risk assessment used in the RCTs, that is based on the diagnosis of admission, does not sufficiently take into account the heterogeneity of medical diseases and the role of concomitant patient-specific risk factors; second, immobilisation per se does not represent a sufficient condition for recommending pharmacologic thromboprophylaxis; third, patient bleeding risk has not been adequately addressed and, therefore, used for patient selection (12).

The 9th edition of the American College of Chest Physicians (ACCP) guidelines for the first time introduced a new approach to patient selection, based on the application of risk assessment models (RAM) (3). The concept behind RAMs is that VTE risk factors are generally cumulative and the majority of patients hospitalised in medical wards harbour more than one risk factor. The proposed RAM to assess VTE risk for the medical population was the PADUA score, which combines patient specific risk factors (e.g. advanced age, obesity, known thrombophilia, previous VTE) and disease specific risk factors (e.g. cancer, heart failure, respiratory failure, reduced mobility) (13). Although there was no validated RAM to assess the individual risk of bleeding, the guidelines panel proposed to consider the IMPROVE bleeding risk score, yet acknowledging this score is complex and not validated, and therefore suggesting to consider patients to have an excessive risk of bleeding if they had multiple risk factors or one risk factor with the strongest association with bleeding (14). Unfortunately, none of available RAM has been extensively and adequately validated till recently (15). Indeed, the model performance in validation studies is often worse than in development studies (12).

In this issue of Thrombosis and Haemostasis, Mahan et al. published the first external validation of any appropriately evidence-derived RAM in acutely ill medical patients (16). They used a large database of 41,486 inpatients from three acute care hospitals to validate the IMPROVE RAM. The seven included VTE risk factors and the assigned points can be summarised by the acronym IMP;P;A;C;T;I;L;I: Immobilisation ≥ 7 days, Previous VTE, Age > 60 years, Cancer, known Thrombophilia, Intensive care / coronary care unit stay, Lower Limb paralysis. In the derivation cohort, a score of 0 to 1 placed patients at low risk of symptomatic VTE (less than 1%), a score of 2 to 3 at moderate VTE risk (1 to 2%), and a score of 4 or more at high VTE risk (> 4.8%) (17). In this study, the incidence of VTE was 0.20% (95% confidence interval [CI] 0.18-0.22), 1.04% (95% CI 0.88-1.25) and 4.15% (95% CI 2.79-8.12) in the low, moderate, and high VTE risk groups, respectively (16). The proportion of patients classified at low, moderate and high VTE risk was 63.3%, 31.1%, and 5.5%, respectively. As the receiver-operating curve was 0.77, we may conclude that another step forward for the correct stratification of VTE risk in medical inpatients has been made.

We are only at the beginning of a new era in VTE prevention. As correctly acknowledged by the authors, this external validation study demonstrates a level 2 of evidence for the validation of a RAM, according to McGinn scale (18). An impact analysis remains necessary in order to reach a level 1 of evidence and to use a RAM in a wide variety of settings with confidence that its use can change clinical behaviour and improve patient outcomes. Concomitantly, it is important to perform

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pharmacologic RCTs using a validated RAM, possibly in combination with newly identified markers of increased VTE risk. In a subgroup analysis of the MAGELLAN trial, patients with higher baseline D-dimer levels (>2 upper limit of normal) resulted to be at increased risk of VTE; the incorporation of a laboratory marker in a well validated RAM has the potential to tailor prevention strategies based on disease-related VTE risk, but also on time-related VTE risk, as recently suggested by another sub-analysis of the MAGELLAN trial (19, 20). In this study, patients with more severe heart failure, as defined by high NT-proBNP plasma concentration, were at increased short-term risk of VTE, whereas elevated D-dimer identified patients a increased mid-term VTE risk (20). Two large ongoing RCTs, the APEX and MARINER studies, that are assessing the role of the direct Xa inhibitors betrixaban and rivaroxaban for the extended-duration VTE prevention in medical inpatients, are for the first time including RAMs and D-dimer to identify high risk medical patients (21, 22). Improvement in patient selection should result in a more appropriate use of thromboprophylaxis, not only for high-risk patients, for whom it is currently underused, but also for low-risk patients, for whom it is often inappropriately prescribed. The IMPROVE RAM confirms that approximately two-thirds of medical inpatients are at low VTE risk (16). In these patients, unnecessary prescription of anticoagulant drugs results in an avoidable increased bleeding risk (16). Adequately validated RAMs can be easily placed in applications for smartphones and tablets, becoming widely and easily available to ameliorate daily clinical activities (23). The use of these applications could help physicians at patient bedside because they are user-friendly, do not need sophisticated software, and can easily manage different RAMs, also those with high number of variables.

The development of a validated RAM for bleeding risk remains the next (and most difficult) unmet clinical need to be addressed by researchers. Ideally, the same RAM should concomitantly assess both bleeding and thrombotic risk to identify patients for whom anticoagulant prophylaxis results in an overall favourable risk-to-benefit ratio.

The new era of VTE prevention in medical inpatients has just started.

Conflicts of interest
None declared.

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