Predicting Venous Thromboembolism in Primary Care

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Venous thromboembolism (VTE) is diagnosed in the outpatient setting in at least 70% of the cases[1,2] and prevention of ambulatory cases might substantially contribute to a reduction of its socio-economic burden.[3,4] Notwithstanding, as we enter the second decade of this millennium, the evidence that was generated after decades of clinical research remains unable to support decision-making beyond in-hospital thromboprophylaxis. Clearly, the exposure to major risk factors for thrombosis is highest during hospitalisation, and this is when the highest absolute rates of VTE are observed. Prophylactic anticoagulation is, therefore, routinely recommended based on the usually favourable benefit-to-risk ratio in this setting.[5] On the other hand, if we turn our attention to primary VTE prevention in the non-hospitalised population, only selected patient groups with active cancer have been targeted by clinical trials in view of their substantial baseline risk of developing VTE.[6,7] Although the VTE risk of individuals without cancer might also suffice for considering primary thromboprophylaxis in primary care, current evidence falls short of quantifying this risk and reliably identifying patients who may benefit from pharmacological preventive strategies.

In this issue of *Thrombosis and Haemostasis*, Dentali et al make a new attempt to identify predictors of VTE in primary care.[8] Their risk assessment model was derived using data from a large Italian database of more than one million adults followed by 1,100 general practitioners. After derivation and internal validation, they performed external validation in an independent cohort used by local authorities for health care assessment. The analysis was conducted as a nested case–control study, where VTE diagnoses were defined by a combination of International Classification of Diseases-9th Edition codes. Control patients who did not develop VTE during same-length follow-up were randomly matched to VTE cases within each risk set. The main finding of the study by Dentali et al is that patients who had recently been hospitalised, admitted to the emergency room, or had suffered fracture, stroke, acute infection, or prior VTE, had an at least twofold higher risk of suffering VTE during follow-up. To make their risk assessment model more practical and facilitate clinical decisions, the authors went further by developing a classifier for patients into the different risk categories.

In a world where new clinical scores are constantly developed, published, and then frequently discarded as clinically irrelevant, the authors must be commended for scrutinising their risk assessment model by determining its discrimination, calibration and potential clinical benefit if it were to be used for thromboprophylaxis.[8] For the readers who are not familiar with these parameters, discrimination corresponds to the probability of correctly classifying patients into those who will and those who will not have the outcome, in this case VTE. Discrimination alone, however, has no clinical utility and is a poor method for comparing risk assessment models.[9] Moreover, the minimum threshold for defining the adequate level of discrimination, as reflected by the concordance statistics (or c-statistics), may largely vary across different clinical settings. In contrast, calibration is a measure of "absolute accuracy" and possibly more important for making individual-level decisions, as it refers to how closely the predicted VTE risk matches the observed VTE risk. In an additional decision curve analysis,[10] the authors provided initial proof that using this model in decision-making concerning thromboprophylaxis might provide a benefit, in terms of both VTE and bleeding risk, compared with treating all patients or treating none.[8]

So, how should these results be interpreted in the context of the available strategies for primary and secondary VTE prevention? Concerning primary prevention, the first important comment on the present study is that the strongest predictors of VTE in primary care were related to recent hospitalisation or to other conditions that would have received thromboprophylaxis anyway based on current standards. Therefore, this model may

TRIALS ON THROMBOPROPHYLAXIS IN AMBULATORY (RECENTLY HOSPITALISED) MEDICALLY ILL PATIENTS

EXCLAIM	ADOPT	MAGELLAN		APEX	MARINER
2010	2011	2013		2016	2018

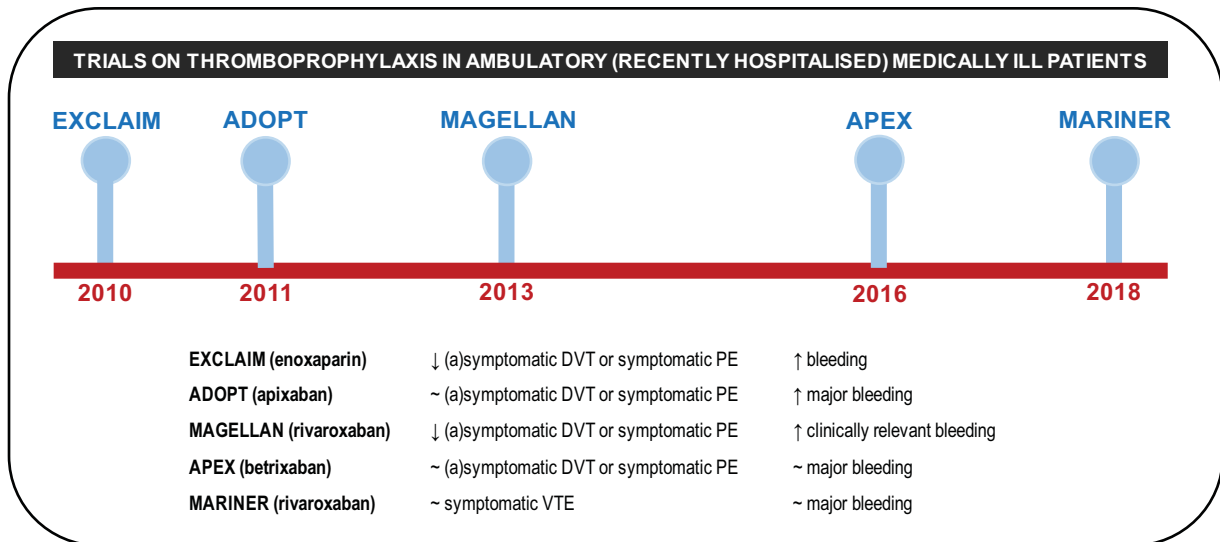|		
EXCLAIM (enoxaparin)	↓ (a)symptomatic DVT or symptomatic PE	↑ bleeding
ADOPT (apixaban)	~ (a)symptomatic DVT or symptomatic PE	↑ major bleeding
MAGELLAN (rivaroxaban)	↓ (a)symptomatic DVT or symptomatic PE	↑ clinically relevant bleeding
APEX (betrixaban)	~ (a)symptomatic DVT or symptomatic PE	~ major bleeding
MARINER (rivaroxaban)	~ symptomatic VTE	~ major bleeding

Fig. 1 Trials on thromboprophylaxis in ambulatory (recently hospitalised) medically ill patients ADOPT, Apixaban Dosing to Optimize Protection from Thrombosis trial; APEX, Acute Medically Ill VTE Prevention With Extended Duration Betrixaban study; DVT, deep vein thrombosis; EXCLAIM, Extended Prophylaxis for Venous ThromboEmbolism in Acutely Ill Medical Patients With Prolonged Immobilization trial; MAGELLAN, Multicenter, Randomized, Parallel Group Efficacy and Safety Study for the Prevention of Venous Thromboembolism in Hospitalized Acutely Ill Medical Patients Comparing Rivaroxaban with Enoxaparin trial; MARINER, Medically Ill Patient Assessment of Rivaroxaban versus Placebo in Reducing Post-Discharge Venous Thrombo-Embolism Risk trial; PE, pulmonary embolism; VTE, venous thromboembolism.

be more helpful for identifying candidates for *extended* thromboprophylaxis than for truly primary VTE prevention. Such an improved selection model may indeed be necessary, particularly since recent major trials (►**Fig. 1**) yielded rather equivocal results on who, among the medically ill patients, should receive extended anticoagulant prophylaxis after discharge from hospital.[11–15]

The second comment relates to the other major predictor that the authors identified was a prior diagnosis of acute VTE. In the era of (low-dose) oral anticoagulation for the long-term secondary prevention of VTE, an increasing number of patients will be candidates for extended anticoagulation after a first episode of acute VTE.[16,17] The results of a meta-analysis of clinical trials showed that the use of non-vitamin K oral anticoagulants for extended anticoagulation was associated with a reduction in overall mortality.[18] Therefore, it is possible that the scenario that general practitioners will face in a few years from now will be much different from that of the present study.

Third, a potential discrepancy between the setting of the current study and evolving clinical scenarios concerns patients with cancer, a factor not recognised in the present study as a potential predictor of VTE in primary care. Several clinical and statistical reasons may explain this phenomenon. The most obvious is that patients with cancer were likely to have already received anticoagulation based on their perceived higher thrombotic risk and therefore were spuriously classified as being "at no risk" for VTE. The same argument may also apply to other established VTE risk factors. A recent practice-based study confirmed that these factors do influence the physicians' decision to opt for prolonged post-discharge prophylaxis.[19]

The results of the study by Dentali et al should be seen as hypothesis generating and necessitate further investigation in the setting of an interventional study. What they highlight is that current preventive strategies appear insufficient to cover the entire spectrum of patients at risk for VTE, since this risk clearly extends beyond the period of hospitalisation. As the burden of VTE remains substantial[20] and global public awareness low,[21] such a tool may serve to attract the attention of general practitioners and stimulate them to increase the level of VTE suspicion, with implications not only for VTE diagnosis and management but also for primary VTE prophylaxis in primary care.

Conflict of Interest
S.B. has received congress and travel payments from Daiichi-Sankyo and Bayer HealthCare, and honoraria from BTG Pharmaceuticals, Bayer HealthCare and Leo-Pharma. S.K. reports grants and nonfinancial support from Bayer AG; grants and personal fees from Boehringer Ingelheim, personal fees from Bayer AG, grants and personal fees from Actelion, Daiichi-Sankyo, and Biocompatibles Group UK, personal fees from Pfizer-Bristol-Myers Squibb and grants and personal fees from MSD, all outside the submitted work.

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