

## **Letter to the Editor**

### **Call to Action to Prevent Venous Thromboembolism in Hospitalized Patients**

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Dear Sirs

I read with interest the formal policy statement from the American Heart Association by Henke and colleagues [1]. It is important that there is renewed interest for both clinical research activities as well as formal policy and guideline development in the population of medically ill patients which is responsible for more than half of all VTE events in the community, with the majority of events occurring in the post-discharge period [2]. While there is clearly underuse of VTE prophylaxis for medically ill patients in hospitalized settings as the authors suggest, this underuse and subsequent lack of treatment effects from hospital-based quality efforts in VTE prevention comes mostly from one simple fact: in US hospitalized settings the average length-of-stay of 4 – 5 days and lack of routine post-discharge thromboprophylaxis (<4% of patients) means that the vast majority of medically-ill patients are not receiving even the minimum duration of thromboprophylaxis (median 10 days) that has established efficacy in earlier hospital-based placebo-controlled randomized trials [2]. Second, the statements made by the authors that extended thromboprophylaxis with the direct oral anticoagulants betrixaban and rivaroxaban were not associated with reduced VTE compared to standard-duration low-molecular-weight heparin are simply false. The MAGELLAN trial revealed a significant reduction in VTE risk with extended-duration rivaroxaban compared to enoxaparin (Relative Risk (RR) 0.77; 95% CI 0.62–0.96) but was associated with an almost 3-fold increase in the risk of major bleeding [3]. A post-hoc analysis of the MAGELLAN trial that excluded approximately 20% of the study population by removing five key bleeding risk factors (bronchiectasis/pulmonary cavitation, active cancer, active gastroduodenal ulcer/history of bleeding within 3 months, and dual antiplatelet therapy) maintained the efficacy of rivaroxaban but reduced major bleed rates by half so that major bleeding was not significantly worse with

rivaroxaban (Day 10, RR 1.19, 95% CI 0.54–2.65; Day 35 RR 1.48, 95% CI 0.77–2.84) [4]. The APEX trial with betrixaban narrowly failed to show efficacy compared to standard-duration enoxaparin for the primary efficacy outcome ( $p=0.054$ ), but a pre-specified analysis provided evidence of a benefit for betrixaban in the total population (RR 0.76; 95% CI 0.63–0.92) and the modified intent-to-treat population for whom there was an evaluable primary efficacy outcome [5]. There was no increase in the risk of major bleeding (0.57% vs. 0.67%,  $p = 0.55$ ). Because of clear evidence of efficacy in the reduction of VTE for medically ill patients, the Food and Drug Administration granted approvals for use of betrixaban and rivaroxaban for the prevention of VTE in-hospital and in the extended post-hospital discharge period. Given the clear efficacy data of the DOACs and very good safety profile, as well as the convenience of oral administration compared to once to thrice-daily injections using heparins, DOACs are becoming a preferred option for both out-of-hospital and extended thromboprophylaxis, as well as a viable option for use in the inpatient setting. Their use in the post-discharge setting may play an important role in the reduction of the burden of VTE in hospitalized patients.

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## Letter to Editor in response to Policy for VTE Prevention paper

We appreciate the letter of Dr. Alex Spyropoulos regarding the AHA Policy Statement 'Call to Action to Prevent Venous Thromboembolism in Hospitalized Patients'. First, we acknowledge and have corrected the factual error related to the timing of follow-up to state that non-inferiority between arms was seen at 10 days, not at 35 days in the MAGELLAN trial. We note that a 23% relative risk reduction in VTE was observed through 35 days with extended rivaroxaban prophylaxis as compared with placebo in medically ill patients, but at the cost of increased bleeding (4.1% vs 1.7%).<sup>1</sup> While we acknowledge that post-hospital thromboprophylaxis may be of benefit, not all trials have found this to be true. In particular, the primary outcomes in the MARINER and APEX trials showed no significant benefit to extended prophylaxis in medical patients,<sup>2, 3</sup> and this has been the finding of several recent meta-analyses as well.<sup>4, 5</sup>

More importantly, the main goal of the Policy Statement is a call for all practitioners who take care of hospitalized medical and surgical patients to increase and consistently perform VTE risk assessment, to provide a standardized and rigorous tracking of preventable VTE, and to increase prescription of appropriate VTE prophylaxis for those most likely to benefit. This paper was not intended to be an exhaustive review of any particular aspect of chemoprophylaxis, such as extended direct oral anticoagulant use in medical patients. We similarly mentioned the indications for extended use in surgical patients as well, summarizing the evidenced based guidelines.

We look forward to helping implement and educate our colleagues on this important topic as it relates to actionable policies.

Peter Henke for the Writing Group

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