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Letter to the Editors-in-Chief

Thromboprophylaxis by rivaroxaban, aspirin, both, or placebo after hospitalization for medical illness

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1. Introduction

There is interest in preventing venous thromboembolism after discharge from medical inpatient status [1,2]. Low-dose aspirin seems to perform as well as low-dose anticoagulant therapy in this indication after discharge following hip and knee replacement [3,4], hospitalizations that also increase venous thromboembolic risk. Medical inpatients taking low-dose aspirin are frequently encountered. Since about half of the 12,019 medical inpatients received low-dose aspirin after discharge in a recent rivaroxaban vs placebo-controlled clinical trial, MARINER [1], we took the opportunity to compare efficacy of taking low-dose aspirin, rivaroxaban, taking both, and taking neither.

2. Study results

After an inpatient stay of 3 to 10 days for a variety of medical illnesses, with subcutaneous low molecular weight heparin or heparin prophylaxis dosed during the hospitalization [1], patients were discharged on either blinded rivaroxaban 10 mg daily or placebo for 45 days. The primary efficacy outcome was a composite of symptomatic venous thromboembolism or death due to venous thromboembolism. The principal safety outcome was major bleeding. Aspirin ≤162 mg/day was allowed. Patients requiring continued or higher-dose anticoagulant therapy were excluded. The Mantel-Haenszel test was used to compare treatments. Exact confidence intervals were calculated by standard methods. The current report was unsponsored.

Altogether, 12,019 patients randomized 1:1 between rivaroxaban or placebo were included in the intention-to-treat efficacy analysis. Approximately 25% of patients were in each of the four re-analyzed treatment groups in Table 1 (Figs. S1 and S2 of the original report [1]). Medical inpatients taking both rivaroxaban and aspirin compared to those taking neither drug after hospital discharge (Table 1) experienced a 41% reduction in venous thromboembolism, from 1.3% for neither, to 0.8% for both, and an absolute reduction of 0.5%, 95% CI 0.0 to 1.0%, $p = 0.042$, number needed to treat 192. Patients taking either aspirin or rivaroxaban alone after discharge experienced apparently identical thrombosis rates, 0.9%, 95% CI 0.6 to 1.3%.

The discharged medical service patients from MARINER we analyzed had been selected to be at particular high risk of venous thromboembolism after discharge [1] so it is noteworthy that taking up to 162 mg of daily aspirin after discharge was associated with subsequent thrombosis at a rate equivalent to that of rivaroxaban, with about equivalent major bleeding. The combination of rivaroxaban and aspirin was associated with a borderline significant reduction in thrombosis compared to patients taking neither. These *p*-values are not adjusted for multiple comparisons.

Could one consider a “transitive property” for thromboprophylaxis based on performance of drugs in other rigorous studies and the data we extract and present here? The formal conclusion of the MARINER study was no significant improvement in efficacy with rivaroxaban because the hazard ratio favoring the overall rivaroxaban group, 0.76, was associated with a non-significant *p*-value. The study report noted a significant benefit for a secondary outcome, reduction in non-fatal venous thromboembolism, hazard ratio 0.44. Rivaroxaban's and aspirin's efficacy in thromboprophylaxis after joint replacement surgery are well-established [3,4]. Outpatient rivaroxaban thromboprophylaxis in discharged medical patients was superior to placebo but its major bleeding event rate was high [5]. Could a reasonable physician consider such prior evidence, review rivaroxaban's limited though non-significant efficacy in the medical patient population from MARINER, and conclude that it probably extends to aspirin, given the precisely parallel results in the large numbers of patients shown in Table 1?

This analysis is hypothesis-generating, with several limitations. Data for fatal vs symptomatic nonfatal VTE was not available to us for the aspirin/no aspirin subgroups, and it is possible there were important differences in fatal VTE, for example, that would favor one treatment over another. Randomization was not stratified by aspirin use, so aspirin-taking patients cannot be assumed to be identical to the non-aspirin taking group and presumably were more tolerant to its adverse effects than the general population. However, the very many aspirin recipients enrolled could legitimately be hypothesized to be at the same or higher thrombosis risk than the 50% of study patients not taking aspirin. This analysis could be clinically relevant to real-world practice because medical inpatients taking low-dose aspirin are frequently encountered –they were half of the study entrants, for example. Since it is unlikely a sponsor will pay to test aspirin alone in a prospective trial of

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Table 1
Efficacy and safety of rivaroxaban alone, aspirin alone, rivaroxaban with aspirin, and placebo (no rivaroxaban, no aspirin) for venous thromboprophylaxis after hospitalization for medical illness (Odds Ratios, OR, with 95% CIs).

	Symptomatic/fatal venous thromboembolism	Major bleeding
Rivaroxaban/no aspirin	26/2848 (0.9%)	8/2833 (0.3%)
95% CI	(0.6–1.3%)	(0.1–0.6%)
OR vs no rivaroxaban/no aspirin	0.71 (0.42–1.20), $p = 0.18$	
Aspirin/no rivaroxaban	28/3046 (0.9%)	6/3032 (0.2%)
95% CI	(0.6–1.3%)	(0.1–0.4%)
OR vs no rivaroxaban/no aspirin	0.72 (0.43–1.20), $p = 0.18$	
Rivaroxaban/aspirin	24/3159 (0.8%)	9/3149 (0.3%)
95% CI	(0.5–1.1%)	(0.1–0.5%)
OR vs no rivaroxaban/no aspirin	0.59 (0.35–0.99), $p = 0.042$	
No rivaroxaban/no aspirin	38/2966 (1.3%)	3/2948 (0.1%)
95% CI	(0.9–1.7%)	(0–0.3%)

this size or larger, is there genuine clinical relevance of these already available data? Rivaroxaban alone at 10 mg/day and aspirin alone up to 182 mg/day for 45 days are associated with equivalent thrombosis rates after discharge—although 95% CIs overlap with those of no rivaroxaban, no aspirin. We cannot comment on the efficacy and safety of low-dose aspirin alone vs betrixaban alone because similar data has not been made available from that study [2].

Forty-five post-discharge days of rivaroxaban 10 mg alone or low-dose aspirin alone appear to be equally ineffective or effective and yield equivalent thromboprophylaxis and safety in higher-risk medical patients after hospital discharge.

Contributions

W Tomkowski and BL Davidson both contributed to concept, design, calculations, analysis, critical writing and revision, and both approved this final version.

Declaration of Competing Interest

W Tomkowski declares Bayer, Sanofi, Pfizer, Alfa-Sigma, Portola, Boehringer-Ingelheim, Aspen Pharma. BL Davidson declares no competing interests.

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Witold Z. Tomkowski[a], Bruce L. Davidson[b,*]
[a] *Cardio-Pulmonary Intensive Care, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland*
[b] *Providence Health System, Seattle, WA, United States of America*
E-mail addresses: w.tomkowski@igichp.edu.pl (W.Z. Tomkowski), brucedavidson@pobox.com (B.L. Davidson).

* Corresponding author.