CLINICAL RESEARCH STUDY

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Contemporary Meta-Analysis of Extended Direct-Acting Oral Anticoagulant Thromboprophylaxis to Prevent Venous Thromboembolism

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ABSTRACT

BACKGROUND: Medically ill patients remain at risk of venous thromboembolism for up to 6 weeks after hospital discharge due to factors such as immobilization and inflammation.

METHODS: We conducted a meta-analysis and systematic review of Phase III randomized controlled trials comparing extended use of direct oral anticoagulation (DOAC) post discharge for venous thromboembolism prophylaxis with placebo.

RESULTS: The primary efficacy outcome (composite of venous thromboembolism and mortality) occurred in 373/13,099 patients in the DOAC group (2.9%) and 477/13,309 patients in the placebo group (3.6%), with an odds ratio (OR) of 0.79 (95% confidence interval [CI], 0.69-0.91). The secondary efficacy outcome (nonfatal symptomatic venous thromboembolism) occurred in 75/15,573 patients in the DOAC group (0.48%) and 120/15,599 in the placebo group (0.77%) with an OR of 0.62 (95% CI, 0.47-0.83). The primary safety outcome (major bleeding) occurred in 90/15,474 patients in the DOAC group (0.58%) and in 47/15,418 patients in the placebo group (0.3%) with an OR of 1.92 (95% CI, 1.35-2.73). The secondary safety (clinically relevant nonmajor bleeding) outcome occurred in 333/15,474 patients in the DOAC group (2.2%) and 191/15,418 patients in the placebo group (1.2%) with an OR of 1.75 (95% CI, 1.46-2.1). The extended use of venous thromboembolism prophylaxis post discharge results in decreased venous thromboembolism events but increased bleeding risk. Our cost-effective analysis of extended DOAC use vs placebo showed superiority of the DOAC group.

CONCLUSION: In conclusion, given the mortality benefit and cost benefit, extended thromboprophylaxis is a beneficial strategy to efficiently reduce the risk of venous thromboembolism.

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KEYWORDS: Direct-acting oral anticoagulants; Medical illness hospitalization; Meta-analysis; Thromboprophylaxis

INTRODUCTION

There are over 36 million medical hospitalizations each year in the United States, with the majority being for acute medical illness.[1] Cancer, chronic obstructive pulmonary disease, congestive heart failure, stroke, and myocardial infarction are some of the most common indications for hospitalization and are, additionally, risk factors for venous thromboembolism.[2] With over 900,000 patients suffering

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from venous thromboembolism each year, excess thrombosis causes a large medical and financial burden to patients and the health care system.[3] Therefore, thromboprophylaxis has become the standard of care for inpatients, typically achieved by administration of subcutaneous unfractionated or low-molecular-weight heparin.[4] Use of inpatient thromboprophylaxis with anticoagulation reduces venous thromboembolism events by 50%-75% without a significant increase in bleeding risk.[4,5]

Prophylaxis during inpatient stay only may not be sufficient to prevent venous thromboembolism. Despite the success of inpatient thromboprophylaxis programs, medically ill patients continue to be at risk of venous thromboembolism after discharge. In one study, 37% of outpatient venous thromboembolism cases occurred in patients who had been hospitalized in the past 3 months. Patients who are hospitalized for an acute medical illness remain at risk of venous thromboembolism for up to 6 weeks after discharge.[6,7] The risk of postdischarge venous thromboembolism in surgical patients is reduced with use of extended thromboprophylaxis.[8] However, studies investigating extended low-molecular-weight heparin administered for a short period after discharge demonstrated an increased risk of bleeding.[9] Thus, extended therapy after discharge has been discouraged except in highest-risk patients, such as after orthopedic surgeries.

The direct acting oral anticoagulants (DOACS) are emerging as an attractive alternative to subcutaneous administration of heparin products, as they may be associated with lower bleeding and also less discomfort and therefore, higher adherence. A recent meta-analysis demonstrated that these agents are as effective, safe, and cost effective as subcutaneous low-molecular-weight heparin for inpatient prophylaxis.[10] Individual DOACs have been evaluated for extended therapy after hospitalization, however, whether there is a class effect of extended duration DOACs on venous thromboembolism, bleeding or a net clinical benefit has not been vigorously evaluated. This systematic review and meta-analysis summarizes the available literature from randomized clinical trials and examines the efficacy and safety of extended venous thromboembolism prophylaxis using rivaroxaban, apixaban, and betrixaban for 30-45 days after discharge from the hospital for an acute medical illness.

CLINICAL SIGNIFICANCE

- When extrapolated to the national level, direct oral anticoagulation thromboprophylaxis for 30-45 days after discharge leads to an estimated net clinical benefit of 3183-3820 lives saved when accounting for fatal bleeding events.
- Extended thromboprophylaxis after discharge is associated with a cost benefit due to decreased thrombotic events.
- Future research directions in patient selection and ideal outpatient prophylaxis duration is needed to maximize benefit and minimize the risk of bleeding.

METHODS

This meta-analysis and systematic review were performed by searching MEDLINE, the Cochrane Central Register of Controlled Trials, and ClinicalTrial.gov databases through October 1, 2018 for the following MESH terms and keywords: Factor Xa inhibitors, rivaroxaban, apixaban, betrixaban, or direct thrombin inhibitor (dabigatran), deep vein thrombosis prophylaxis, thromboprophylaxis, and "randomized clinical trial." This was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guideline.[11] We restricted our database search to English language, phase III randomized clinical trials in humans. The originally screened articles and relevant review articles were reviewed for reference studies as well. The Supplementary Methods section details the search methodology (Appendix). To be eligible, the studies must have met the following criteria: 1) randomized clinical trial design; 2) use of DOAC for venous thromboembolism prophylaxis in patients after hospital discharge for 30-45 days; 3) report the incidence of primary endpoints of total venous thromboembolism, total mortality, major bleeding, and clinically relevant major and nonmajor bleeding as detailed below; 4) median follow-up duration of 5 weeks. The trials were independently screened and assessed for eligibility using predefined inclusion criteria by 2 investigators (VB and AAL). Full articles of relevant topics were assessed by each investigator for inclusion in the meta-analysis and disagreements were resolved through discussions between the 2 investigators. All data were obtained from the published articles. Cochrane's Collaboration's risk of bias tool was used for quality assessment.[12]

These trials include medical patients who were ≥40 years of age, at risk of venous thromboembolism, and hospitalized due to the presence of the following acute medical conditions: heart failure New York Heart Association (NYHA) class III or IV, active cancer, acute ischemic stroke, acute respiratory insufficiency, and acute infectious and inflammatory diseases, including acute rheumatic diseases. Patients must have at least one of the following risk factors for venous thromboembolism: severe varicosity, chronic venous insufficiency, history of cancer, history of venous thromboembolism, history of heart failure (NYHA class III/IV), thrombophilia (hereditary or acquired), hormone replacement therapy, recent major surgery or serious trauma (past 6-12 weeks), morbid obesity (body mass index >35 kg/m^2), age ≥75 years, or acute infectious disease contributing to hospitalization. The exclusion criteria consist of the following: active bleeding or high bleeding risk, contraindication to the use of DOACs, abnormal liver enzymes, renal failure, pregnancy or breastfeeding, concomitant medications with possible interactions, requirement for

continued anticoagulation or planned intermittent pneumatic compression. Comprehensive inclusion and exclusion criteria for included studies are listed in Supplementary Tables 1-4 (available online).

This study analyzed 2 efficacy and 2 safety variables. The primary efficacy variable was the composite endpoint of total venous thromboembolism and venous thromboembolism-related death. The secondary efficacy endpoint was the incidence of nonfatal symptomatic venous thromboembolism. The treatment safety primary outcome was determined through the incidence of major bleeding. The safety secondary outcome was clinically relevant nonmajor bleeding. Major bleeding was defined as bleeding that is fatal, in a critical organ, associated with a decrease in hemoglobin concentration of >2 g/dL, requiring the transfusion of 2 or more packed or whole blood units, or that lead to re-intervention at the surgical site or discontinuation of the study drug. Clinically relevant nonmajor bleeding was defined as overt bleeding, not meeting the criteria for major bleeding that is associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary/permanent) cessation of the study treatment, or associated with discomfort for the patient such as pain or impairment of activities of daily life.

The random-effects model based on DerSimonian and Laird's[13] meta-analytic statistical method was used to calculate summary estimates as odds ratios (ORs) with 95% confidence intervals (CI). The random-effects model was used to assess for effect sizes due to concern for heterogeneity between included trials. Sensitivity analyses were performed using the one-study-removed and cumulative analyses methods to show how the summary estimate changes if the study that has the largest effect size is removed. Egger's regression test and visual inspection of funnel plot were used to assess for potential publication bias.[12] P value of $<.05$ was used for the statistical level of significance. The Comprehensive Meta-analysis version 3.0 software (Biostat, Inc., Englewood, NJ) was used for all statistical analyses.

We used probabilities of venous thromboembolism and bleeding from the included studies and direct cost calculations from Spyropoulos and Lin,[14] Mercaldi et al,[15] Saloner et al,[16] and Moran[17] to perform cost-effective analysis. When considering rivaroxaban 10 mg daily for 45 days, the thromboprophylaxis cost is $450 per patient.[18] Data from one of the included studies were excluded because inpatient and postdischarge events were not reported separately.[19] The efficacy endpoints that were analyzed include venous thromboembolism-related death, pulmonary embolism, and nonfatal, symptomatic deep vein thrombosis. The safety endpoints were fatal bleeding, nonfatal major bleeding, and clinically relevant nonmajor bleeding. Decision tree analysis was performed using the online software SilverDecisions 0.9.0.[20]

RESULTS

This systematic review yielded 4 large-scale, published, phase III randomized clinical trials that compare DOACs to placebo for postdischarge thromboprophylaxis (30-45 days). These studies are MAGELLAN,[21] ADOPT,[22] APEX,[19] and MARINER[23] (Tables 1 and 2). A total of 26,408 patients who received either DOAC or placebo for extended thromboprophylaxis after hospital discharge are included in this

Table 1 Study Details

Study	Inpatient Prophylaxis (mg)	Days of Inpatient Prophylaxis	Postdischarge Prophylaxis (mg)	Days of Postdischarge Prophylaxis
ADOPT	Enoxaparin 40	6	Apixaban 2.5 BID	30
MAGELLAN	Enoxaparin 40	10	Rivaroxaban 10 daily	35
APEX	Enoxaparin 40	10	Betrixaban 80 daily	35-42
MARINER	Unspecified	Unspecified	Rivaroxaban 10 daily	45

BID = twice a day.

Table 2 Study Demographics

Study		Age in Years (Mean ± SD/Median)	Sex (Males) n (%)	Race (Whites) n (%)	Reason for Hospitalization n (%)		
					Congestive Heart Failure	Acute Respiratory Infection	Infection
ADOPT	DOAC (3255)	66.8 ± 12	1626 (50%)	2474 (76%)	1270 (39%)	1208 (37%)	701 (22%)
	Placebo (3273)	66.7 ± 12	1577 (48%)	2476 (76%)	1246 (38%)	1213 (37%)	746 (22%)
MAGELLAN	DOAC (4050)	71	2253 (56%)	2784 (69%)	1308 (32%)	1105 (27%)	1854 (46%)
	Placebo (4051)	71	2136 (53%)	2744 (68%)	1312 (32%)	1163 (29%)	1828 (45%)
APEX	DOAC (3759)	76.6 ± 8.46	1705 (45.4%)	3503 (93.2%)	1677 (44.6%)	448 (11.9%)	1112 (29.6%)
	Placebo (3754)	76.2 ± 8.31	1720 (45.8%)	3518 (93.7%)	1672 (44.5%)	474 (12.6%)	1058 (28.2%)
MARINER	DOAC (6007)	69.7	3130 (52.1%)	5782 (96.3%)	2435 (40.6%)	1575 (26.2%)	1048 (17.5%)
	Placebo (6012)	69.7	3154 (52.5%)	5808 (96.6%)	2399 (39.9%)	1611 (26.8%)	1045 (17.4%)

DOAC = direct oral anticoagulation.

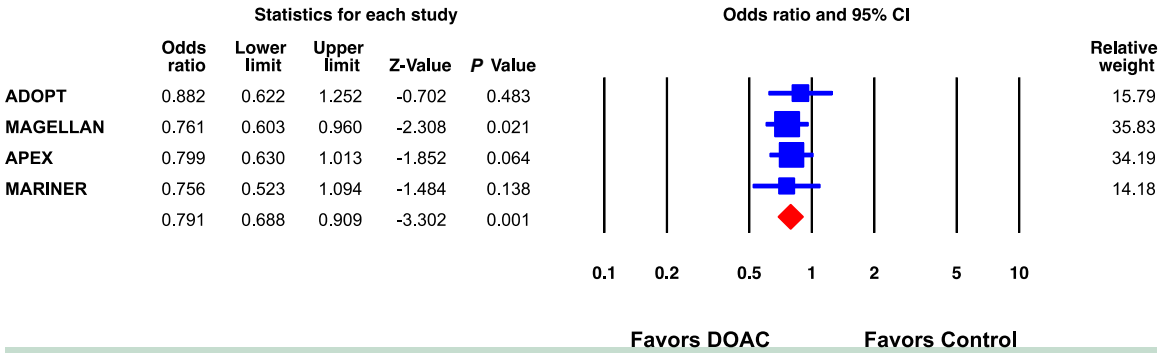

Figure 1 Primary outcome (venous thromboembolism or mortality) in extended venous thromboembolism prophylaxis in 26,408 patients; odds ratio 0.79 ($P < .01$). CI = confidence interval; DOAC = direct oral anticoagulation.

study. The primary efficacy outcome (composite of venous thromboembolism or mortality) occurred in 373/13,099 patients in the DOAC group (2.85%) and 477/13,309 patients in the placebo group (3.58%), with an OR of 0.79 (95% CI, 0.69-0.91, $P < .01$) (Figure 1). The secondary efficacy outcome (nonfatal symptomatic venous thromboembolism) occurred in 75/15,573 patients in the DOAC group (0.48%) and 120/15,599 in the placebo group (0.77%) with an OR of 0.62 (95% CI, 0.47-0.83, $P < .01$) (Figure 2). The primary safety outcome (major bleeding) occurred in 90/15,474 patients in the DOAC group (0.58%) and in 47/15,418 patients in the placebo group (0.30%), with an OR of 1.92 (95% CI, 1.35-2.73, $P < .01$) (Figure 3). The secondary safety outcome (clinically relevant nonmajor bleeding) occurred in 333/15,474 patients in the DOAC group (2.15%) and 191/15,418 patients in the placebo group (1.24%), with an OR of 1.75 (95% CI, 1.46-2.10, $P < .01$) (Figure 4). The numbers needed to treat with a DOAC after discharge to prevent a nonfatal symptomatic venous thromboembolism event and a fatal pulmonary embolism are 345 and 899 patients, respectively. When considering fatal bleeding events, the number needed to harm with DOAC use is 3089, while the number needed to harm for clinically relevant nonmajor bleeding events is 110 patients. Sensitivity analyses using

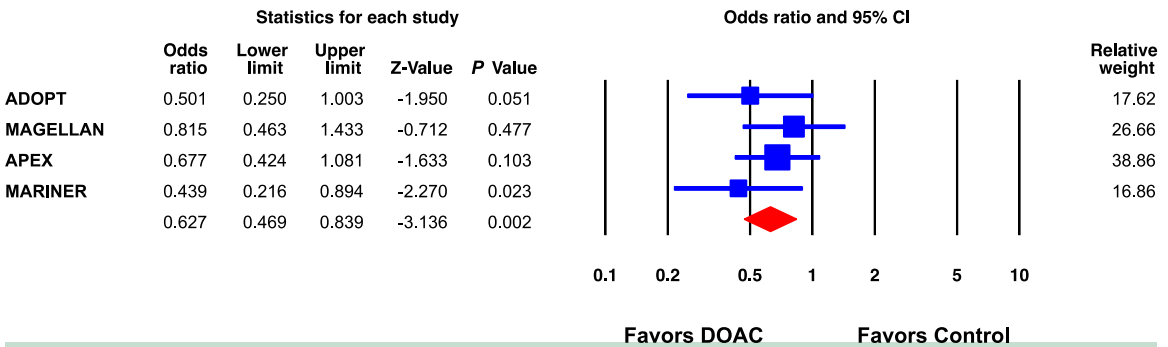

Figure 2 Major bleeding in extended venous thromboembolism prophylaxis in 30,892 patients; odds ratio 1.92 ($P < .01$). CI = confidence interval; DOAC = direct oral anticoagulation.

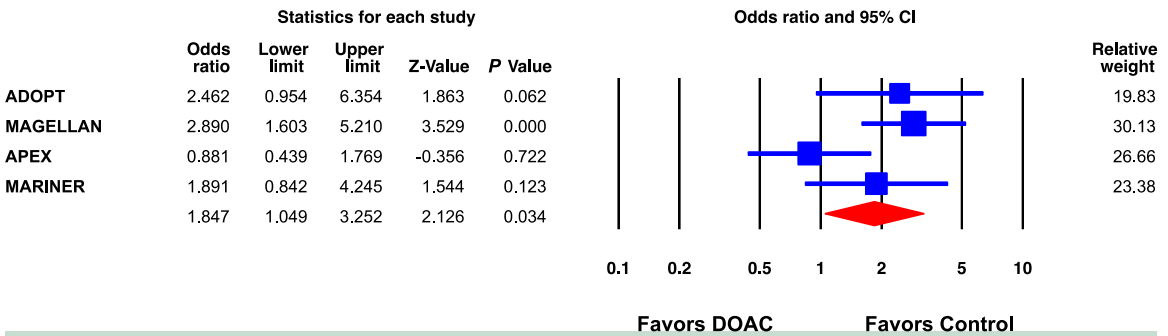

Figure 3 Secondary outcome (nonfatal symptomatic venous thromboembolism) in extended venous thromboembolism prophylaxis in 32,072 patients; odds ratio 0.62 ($P < .01$). CI = confidence interval; DOAC = direct oral anticoagulation.

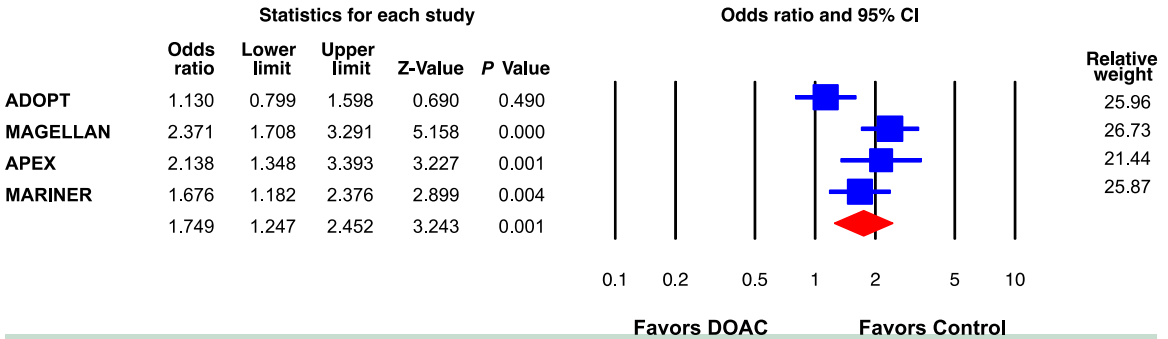

Figure 4 Clinically relevant nonmajor bleeding in extended venous thromboembolism prophylaxis in 30,892 patients; odds ratio 1.75 ($P < .01$). CI = confidence interval; DOAC = direct oral anticoagulation.

the "one study removed" or cumulative analysis methods demonstrated consistency in the outcome measures and no significant changes in the summary OR estimates for any outcome assessed (Supplementary Figures 1 and 2, online). In addition, no clear evidence of publication bias was observed on visual inspection of the Funnel plot. Egger's regression test did not show significant risk of publication bias.

The Decision Tree analysis was performed by considering that hospitalization for pulmonary embolism costs, on average, $17,064, and hospitalization due to major bleeding costs $16,837.[14,15] Additionally, we took into consideration the value of a statistical life of $9.1 million per patient life.[17] We compared bleeding outcomes (fatal bleeding, major bleeding, clinically relevant nonmajor bleeding) and venous thromboembolism events (venous thromboembolism-related death, pulmonary embolism, nonfatal symptomatic deep vein thrombosis) for both the placebo group and the DOAC group to determine the cost-effectiveness of extended DOAC use in medically ill patients. Our study showed superiority of the DOAC arm of the analysis with a cost savings of $5686.39 per patient (Figure 5). Even though the cost of rivaroxaban is $450 per patient for 45 days of anticoagulation,[18] the cost saved from decreased complications and fatalities resulted in cost savings with extended DOAC use.

The meta-analysis data were extrapolated to a national level by considering the implementation of postdischarge thromboprophylaxis with DOAC in all medically ill, hospitalized patients. Additionally, the number of fatal venous thromboembolism and bleeding events were determined from the original study data and expressed as the net clinical benefit. When extrapolated to a national level, the total number of fatal bleeding events is much lower than the number of fatal pulmonary embolism events (1532-1838 vs 4715-5658). Translated to annual medical hospitalizations in the United States, this would result in 3183 to 3820 lives saved per year if extended thromboprophylaxis with a DOAC were implemented nationally after discharge. When accounting for only direct health care costs, this program will cost $4.66 billion annually (Table 3 and Supplementary 5). Therefore, the cost of each prevented fatal venous thromboembolism is $1.2 million, which is less than the value of a statistical life per person of $9.1 million.

DISCUSSION

Venous thromboembolism in hospitalized patients and in the immediate posthospitalization period is a major cause of increased morbidity and mortality. While inpatient thromboprophylaxis has been standard of care, extended duration prophylaxis has not been routinely adopted, largely due to concern for bleeding and uncertainty of clinical benefit. Indeed, current guidelines recommend against extended venous thromboembolism prophylaxis in medically hospitalized patients due to the increased risk of bleeding.[4] Our meta-analysis of randomized clinical trials with extended duration DOACs demonstrates that short-term (30−45-day) outpatient DOAC therapy in medically ill patients has a net clinical benefit driven by decreases in mortality and venous thromboembolism events despite higher risk of bleeding. These findings suggest an important niche for DOAC therapy that can be optimized by additional clinical studies examining dose and duration.

When the results of this meta-analysis were extrapolated to a national level, we found that there is a net clinical benefit with implementation of extended thromboprophylaxis. While there is a large number of total bleeding events, 86% of these events are clinically relevant nonmajor bleeding, and <1% are fatal bleeds. In contrast, 63% of total venous thromboembolism events are fatal venous thromboembolism-related events. Thus, there is a mortality benefit with extended venous thromboembolism prophylaxis.

Both venous thromboembolism and bleeding events contribute to high costs for the health care system. The Decision Tree analysis shows a cost-effectiveness of DOAC extended thromboprophylaxis vs placebo, with a savings of $5686.39 per patient. Additionally, these data were extrapolated to the national level, which determined that the cost of extended thromboprophylaxis is $4.66 billion annually, but the cost saving of prevented fatal pulmonary embolism is $51 billion. Based on these estimates of cost-effectiveness

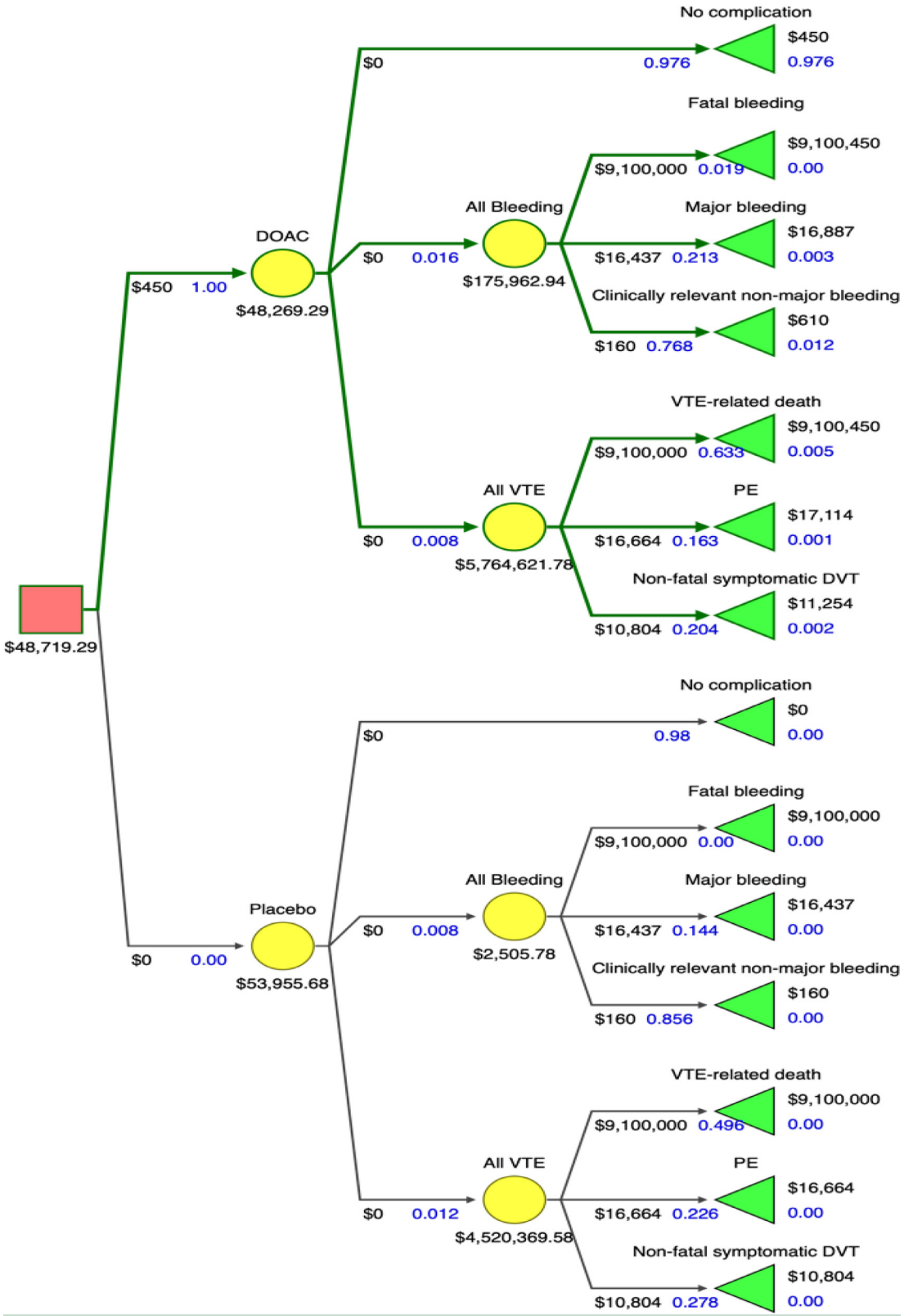

Figure 5 Cost-effective analysis of extended venous thromboembolism prophylaxis vs placebo showing dominance of DOAC arm. Beginning on the right side, each event has a corresponding cost and event rate below the event. Moving to the left, the total cost and event rates for all bleeding and all venous thromboembolism events are shown in both the DOAC and placebo arms. The DOAC arm has an additional $450 added into the cost based on the price of a 45-day supply of rivaroxaban 10 mg. Taking into account the cost of medication and complications, the price per patient per thromboprophylaxis period is located below each arm. The DOAC arm is dominant with a cost savings of $5686.39. DOAC = direct oral anticoagulation; DVT = deep venous thromboembolism; PE = pulmonary embolism; VTE = venous thromboembolism.

Table 3 Cost-Effective Analysis Extrapolated to the National Level, Per Year

Variable	Total n
Nationally eligible medically hospitalized patients	5,040,000-6,048,000
Symptomatic venous thromboembolism prevented	20,401-24,482
Major bleeding events	11,130-13,357
Clinically relevant non-major bleeding events	25,804-30,965
Fatal bleeding events	1532-1838
Fatal pulmonary embolism prevented	4715-5658
Net clinical benefit in lives saved	3183-3820
Variable	Cost $
Cost of preventing one nonfatal symptomatic venous thromboembolism with rivaroxaban	Approximately $111,150-$160,550
Annual national cost of extended oral thromboprophylaxis	Approximately $2.27-3.93 billion annually
Cost saving of prevented symptomatic venous thromboembolism	$245-490 million (using $15K, ~$367 million)
Cost of major bleeding	$200-668 million (using $30K, ~$401 million)
Cost of clinically relevant non-major bleeding	$31-62 million
Cost of fatal bleeding	$17 billion
Cost saving of prevented fatal pulmonary embolism	$51 billion
Total cost of extended thromboprophylaxis	$4.66 billion annually

on a small and large scale, it would be beneficial to our health care system to prescribe extended thromboprophylaxis with DOACs in medically appropriate patients.

While our analysis demonstrated net clinical benefit of extended DOAC therapy, the strategy is associated with higher bleeding. It is possible that higher bleeding could be mitigated by reducing the length of extended therapy, adjusting doses, and targeted patient selection. A limitation of our analysis is that patient outcomes were reported only at the end of the extended DOAC period, which was between 30 and 45 days after discharge. Therefore, conclusions can only be drawn about the use of DOACs for the entirety of the extended thromboprophylaxis period. It would be beneficial to see Kaplan-Meier curves of these data to determine if there is an earlier cutoff point where the risk of venous thromboembolism is significantly greater than the risk of bleeding. This could allow for optimization of the extended DOAC period in order to minimize both bleeding and venous thromboembolism risk. While there already appears to be a benefit of extended thromboprophylaxis for 30 to 45 days, identifying a more specific duration of therapy could increase implementation of extended thromboprophylaxis programs and provide the highest value to patients.

In conclusion, this meta-analysis of randomized controlled trials evaluates the efficacy and safety of the extended use of thromboprophylaxis in medically ill patients. It also evaluates the cost-effectiveness of such a program on both a small and national scale. This study indicates the benefits of extended thromboprophylaxis for medically ill patients but requires further research into the timing, dose, and optimal patient population to receive thromboprophylaxis.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2019.12.056.

APPENDIX

Supplementary Table 1 Individual Inclusion and Exclusion Criteria for MAGELLAN 2013

Inclusion Criteria	Exclusion Criteria
Age ≥40 years • Patients at risk of VTE hospitalized for the following acute medical conditions: - HF, NYHA class III or IV - Active cancer - Acute ischemic stroke - Acute infectious and inflammatory diseases, including acute rheumatic diseases - Acute respiratory insufficiency • Patients with at least one additional risk factor for VTE: - Severe varicosis - Chronic venous insufficiency - History of cancer - History of VTE - History of HF (NYHA class III/IV) - Thrombophilia (hereditary or acquired) - Recent major surgery or serious trauma (6-12 wk) - Hormone replacement therapy - Advanced age ≥75 years - Morbid obesity (body mass index 35 kg/m^2) - Acute infectious disease contributing to hospitalization • Additional risk factor not required for patients with: - Heart failure NYHA class III/IV with previous hospitalizations for heart failure NYHA class III/IV or chronic NYHA class III/IV status - Active cancer - Acute ischemic stroke with lower extremity paresis or paralysis - Anticipated complete immobilization for 1 d during the hospitalization and anticipated decreased level of mobility for ≥4 d after randomization in any type of care setting and additional anticipated ongoing decreased mobility thereafter - Hospitalized <72 h prior to randomization	• Contraindications for the use of the LMWH enoxaparin • Clinically significant bleeding, within 30 d of randomization • Major surgery, biopsy of a parenchymal organ, ophthalmic surgery, or serious trauma within 6 wk prior to randomization • A presenting diagnosis for which surgery is intended during hospitalization • Known coagulopathy or bleeding diathesis or an INR >1.5 at the time of screening unrelated to VKA therapy • History of hemorrhagic stroke at any time in the past, evidence of primary intracranial hemorrhage • Recent severe head trauma within 30 d of randomization • Known intracranial neoplasm, cerebral metastases, arteriovenous malformation, or aneurysm • Known allergy to rivaroxaban or its excipients • Severe renal insufficiency • Known significant liver that would require study medication discontinuation • Known HIV infection at screening • Sustained uncontrolled systolic BP of 180 mm Hg or diastolic BP of 100 mm Hg at time of screening despite treatment • History of ongoing drug or alcohol abuse • Cardiogenic or septic shock with the need for vasopressor(s) • Pregnancy or breastfeeding or any plan to become pregnant during the study • >2 d of prophylactic use of anticoagulants • Systemic treatment with more than 2 doses of strong inhibitors of cytochrome P450 3A4, such as ketoconazole or protease inhibitors, within 4 d prior to randomization or planned treatment during the time period of study drug administration • Indication for fibrinolysis or need for continued treatment with anticoagulant agents for more than 14 d • Treatment with or use of mechanical thromboprophylaxis (eg, pneumatic compression devices, foot pumps) for VTE

BP = blood pressure; HF = heart failure; HIV = human immunodeficiency virus; INR = international normalized ratio; LMWH = low-molecular-weight heparin; NYHA = New York Heart Association; VKA = vitamin K antagonist; VTE = venous thromboembolism.

Supplementary Table 2 Individual Inclusion and Exclusion Criteria for ADOPT 2011

Inclusion Criteria	Exclusion Criteria
Age ≥40 y were considered for participation in the study if they were hospitalized for: • congestive heart failure, • acute respiratory failure, • infection (without septic shock), • acute rheumatic disorder, or inflammatory bowel disease and had an expected hospital stay of at least 3 d. Except for patients with congestive heart failure or respiratory failure, eligible patients had to have at least one of the following additional risk factors: • an age of 75 years or older, • previous documented venous thromboembolism or a history of venous thromboembolism for which they received anticoagulation for at least 6 wk, • cancer, • a body mass index of 30 or more, • receipt of estrogenic hormone therapy, • or chronic heart failure or respiratory failure. In addition, all patients had to be moderately or severely restricted in their mobility.	A confirmed VTE; a disease requiring ongoing treatment with a parenteral or OAT; active liver disease, anemia or thrombocytopenia; severe renal disease; a known or suspected allergy to enoxaparin; or prior HIT or if they were taking 2 or more antiplatelet agents or aspirin at a dose higher than 165 mg per day. Patients were also excluded if they had undergone a surgical procedure in the previous 30 d that might be associated with a risk of bleeding, had received anticoagulant prophylaxis for VTE in the previous 14 d, were actively bleeding or were at high risk for bleeding; invasive procedures planned or scheduled during the treatment period. A hemoglobin level of <9 g/dL, a platelet count of <100,000/mL^3, an alanine or aspartate aminotransferase level more than twice the upper limit of the normal range, or direct or total bilirubin levels more than 1.5 times the upper limit of the normal range; women who might become pregnant, were pregnant, were breastfeeding, or were unwilling or unable to use an acceptable method of contraception were not eligible.

HIT = heparin-induced thrombocytopenia; OAT = oral anticoagulation; VTE = venous thromboembolism.

Supplementary Table 3 Individual Inclusion and Exclusion Criteria for APEX 2016

Inclusion Criteria	Exclusion Criteria
Male or female patients aged ≥40 years. At least one of the following as the cause of the acute hospitalization: • heart failure • respiratory failure • infectious disease • rheumatic disease • ischemic stroke Any one of the following: • age 40-59 years and a D-dimer level at least 2 times the upper limit of normal and a history of VTE (DVT or PE) or cancer (excluding nonmelanoma carcinoma of the skin) or • age 60-74 y and an elevated D-dimer level at least 2 times the upper limit of normal or • age ≥75 y - Patients have been severely immobilized for 24 h or are anticipated to be severely immobilized for 24 h. Severely immobilized means patients are confined to a bed or chair for the majority of the day and can only be independently mobile to the in-room toilet. In-bed/chair physical therapy is permitted. - After 24 h of severe immobilization, patients are anticipated to be severely immobilized or moderately immobilized for 3 or more d. Moderately immobilized means patients can be independently mobile to the in-room or ward toilet; can be mobilized by physical therapy or nursing staff; and can be off-ward with assistance. - Hgb ≥10.0 g/dL during current presentation prior to randomization. A single value of Hgb < 10.0 g/dL does not disqualify a patient. Hgb may be repeated after initial stabilization, eg, after diuresis in patients with acute decompensated heart failure, or - Hgb ≥ 9.5 g/dL from 2 consecutive blood samples taken on consecutive d with stable or rising (ie, not falling) values. - Expected total length of current hospitalization ≥3 d - Enrollment occurs <96 h after hospitalization/presentation (eg, in Emergency Department) for acute medical illness. - Women of childbearing potential must have a negative serum pregnancy test prior to randomization and must be willing to use an acceptable method of contraception to avoid pregnancy throughout the study. Acceptable methods of contraception include bilateral tubal ligation (women), vasectomy (men), oral contraceptive (women), contraceptive patch, anovulants without estrogen, intradermal contraceptive implant with progesterone, progestogen injections every 3 mo or barrier methods (intrauterine device, diaphragm, female condom, male condom). - Abstinence (as part of the patient current lifestyle to choose not to have sex at all) is an acceptable form of contraception, only insofar as patients agree to use another acceptable method of birth control, preferably a barrier method. - Periodic abstinence (trying to check your chances of becoming pregnant by the calendar, ovulation, postovulation or sympto-thermal (checking temperature) methods, and withdrawal are not acceptable methods of contraception. - Signed informed consent form must be present. Patients will be	• Unable to receive nourishment by enteral administration (eg, by mouth, feeding tube, PEG tube). • Anticipated need for prolonged anticoagulation during the trial. • Life expectancy <8 wk • In the opinion of the Investigator, it will not be possible to obtain an adequate bilateral compression ultrasound sonography (CUS) evaluation (eg, patients with above-the-knee amputations, some patients with lower limb lymphoedema or obesity that prevents adequate compression) • Patients unwilling or unable to comply with study procedures (including the Visit 3 ultrasound procedure) or study medications. • Low body weight <45 kg.History of clinically significant bleeding (ie, requiring medical attention) within 6 mo prior to enrollment. • History of any significant gastrointestinal, pulmonary, or urogenital bleeding, ongoing chronic peptic ulcer disease or ongoing or acute gastritis within 2 years prior to enrollment. • Admitting or concomitant diagnosis having resulted in or likely to require major surgery (eg, one in which a body cavity is surgically entered) within 3 mo prior to enrollment or while on study, or other invasive procedure performed within 3 mo prior to enrollment or while on study. • Ophthalmic surgery or biopsy of a parenchymal organ within 3 mo prior to enrollment. Known history of bronchiectasis (as defined by dilation of the bronchi and associated with bloody sputum in patients with chronic pulmonary disease) or active lung cancer; however, lung cancer patients posttreatment who have no evidence of residual disease may be enrolled. • End stage renal disease with CrCl <15 mL/min, or requiring dialysis, or likely to require dialysis within 3 mo of enrollment. • History of: ○ spontaneous intracranial (IC) bleeding within 3 y prior to enrollment or ○ concurrent IC bleeding including hemorrhagic stroke [or clinical presentation consistent with IC bleeding, if computed tomography (CT)/magnetic resonance imaging not available] • History of severe head trauma or other severe physical trauma within 3 mo prior to enrollment • Known intracranial lesions, including neoplasm, metastatic disease, arteriovenous malformation, or aneurysm. • Has severe renal insufficiency (ie, CrCl between >15 mL/min and <30 mL/min) and • requires a concomitant use of a strong P-gp inhibitor (See Appendix B). • Contraindication to anticoagulant therapy: ○ acquired or inherited bleeding diathesis or coagulopathy ○ bacterial endocarditis ○ uncontrolled arterial hypertension (>200 mm Hg systolic or 110 mm Hg diastolic) at 2 consecutive readings ○ platelet count <100,000 mm^3, or activated partial thromboplastin time >1.4 × ULN or INR >1.4, or requirement for thrombolytic therapy ○ contraindication to low-molecular-weight heparins (LMWH) ○ Known abnormality of liver function tests [>3x ULN for serum glutamic-oxaloacetic transaminase/aspartate

Supplementary Table 3 (*Continued*)

Inclusion Criteria	Exclusion Criteria
consented prior to beginning screening procedures; however, once consent is obtained, a "look back" period is allowable to assess eligibility criteria.	aminotransferase, serum glutamate pyruvate transaminase/ alanine transaminase, or alkaline phosphatase, or $> 2 \times$ ULN for total bilirubin in the absence of Gilbert's syndrome], active liver disease, or hepatic dysfunction (eg, cirrhosis). • Known uncontrolled human immunodeficiency virus (HIV) infection, [ie, severely neutropenic (ANC <500/mm^3) or anticipated to develop severe neutropenia during the study treatment period due to prior or planned chemotherapy, or have HIV with CD4 count < 100/mm^3 within 6 mo prior to enrollment] or known complication of HIV infection (eg, *pneumocystis carinii* pneumonia, Kaposi sarcoma) at screening. Patients with stable HIV infection on adequate antiviral medication are eligible for enrollment, although they may require the reduced dose of betrixaban if their antiviral therapy includes a strong P-gp inhibitor (See Appendix B). • Concurrent or history of alcohol or drug abuse within 1 y prior to enrollment. • Shock with persistent systolic BP <90 mm Hg or requiring pharmacological support of blood pressure. • History of hypersensitivity to either of the study articles or any component of their formulations (enoxaparin or betrixaban), including heparin-induced thrombocytopenia. • Pregnancy or breastfeeding or any plan to become pregnant during the study. • Concomitant dual antiplatelet therapy daily [any 2 of the following: aspirin, dipyridamole, or any thienopyridine (ie, clopidogrel, prasugrel, ticlopidine, ticagrelor)]. However, patients receiving a fixed combination of very low-dose aspirin (<50 mg) and persantine products (eg, Aggrenox) may be enrolled. • Greater than 96 h of administration of the following anticoagulants immediately prior to receiving study treatment: ○ enoxaparin or another LMWH ○ fondaparinux ○ injections or infusions of unfractionated heparin • Cannot have received any oral anticoagulant within 96 h immediately prior to the beginning of study treatment (eg, vitamin K antagonist, direct fXa inhibitors, direct thrombin inhibitors). • Indication for fibrinolysis or thrombolysis or having received such therapy within 30 d prior to enrollment. • Use of bevacizumab (Avastin) or similar antiangiogenic therapy within 6 mo prior to enrollment or planned use during the study period. • Use of experimental drugs or devices within 30 d prior to screening. • Patients who were previously randomized in the study cannot be enrolled again at a later date. Unconscious patients will not be enrolled in the trial.

ANC = absolute neutrophil count; CrCl = creatinine clearance; DVT = deep venous thromboembolism; Hgb = hemoglobin; PE = pulmonary embolism; PEG = percutaneous endoscopic gastrostomy; P-gp = P glycoprotein; ULN = upper limits of normal; VTE = venous thromboembolism.

Supplementary Table 4 Individual Inclusion and Exclusion Criteria for MARINER 2018

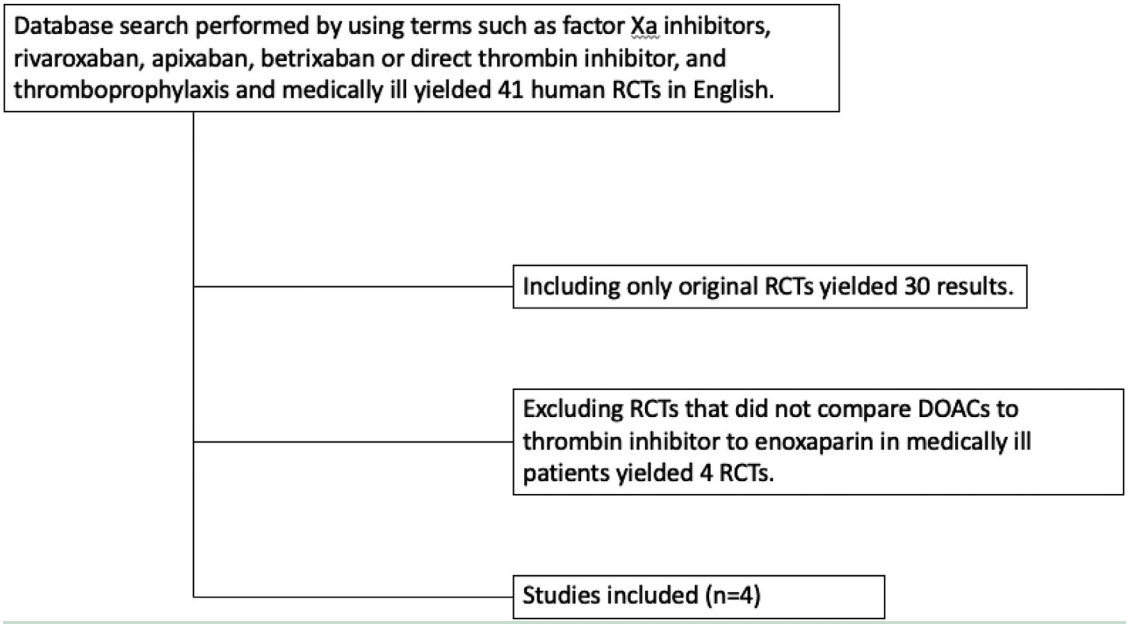
Inclusion Criteria	Exclusion Criteria
Patients were considered if they were ≥40 y old with a hospital course between 3 and 10 d with medical illnesses including: • Heart failure • Acute respiratory insufficiency or acute exacerbation of COPD • Acute ischemic stroke • Acute infectious disease • Inflammatory disease, including rheumatic disease Patient must be at increased risk of VTE according to total modified IMPROVE VTE Risk Score. • IMPROVE score ≥4 • IMPROVE score 2-3 and a D-dimer >2 times ULN Modified IMPROVE VTE Risk Score • Previous VTE − 3 points • Known thrombophilia − 2 points • Current lower limb paralysis or paresis − 2 points • History of cancer − 2 points • ICU/CCU stay − 1 point • Complete immobilization ≥1 day − 1 point • Age ≥60 y − 1 point Patient must have life expectancy ≥3 mo. Inpatient thromboprophylaxis must not exceed 15,000U per day for unfractionated heparin and 5000U per day for LMWH. Patient must sign informed consent.	• Bleeding within 3 mo • Major surgery, biopsy of parenchymal organ, ophthalmic surgery or serious trauma within 4 wk • Planned surgery during trial • History of coagulopathy or bleeding diathesis or INR >1.5 • History of hemorrhagic stroke or intracranial bleeding • History of intracranial neoplasm, cerebral metastases, AV malformation or aneurysm • Active gastroduodenal ulcer within 3 mo or known AV malformation of GI tract • Platelet count <75 × 109 cells/L • Active cancer • Medical condition that requires anticoagulation • Above-knee lower extremity amputation • Severe renal insufficiency • Significant liver disease • Known HIV • Systolic blood pressure ≥180 mm Hg or diastolic blood pressure ≥100 with treatment • Current drug or alcohol abuse • Current cardiogenic or septic shock requiring vasopressors during hospitalization • History of IVC filter • Bronchiectasis or cavitary tuberculosis or other pulmonary conditions at risk of bleeding • P-gp and CYP3A4 inhibitor use within 4 d of randomization • P-gp and CYP3A4 inducer use within 7 d of randomization • Fibrinolysis during hospitalization • Antiplatelet use during hospitalization • Women of childbearing age without contraception, pregnant or breastfeeding • Use of study drug or device within 30 d • Use of NSAIDs during hospitalization • Patient unwilling or unable to complete study protocol • Patient is employee of investigator or study site

AV = atrioventricular; CCU = cardiac care unit; COPD = chronic obstructive pulmonary disease; GI = gastrointestinal; HIV = human immunodeficiency virus; ICU = intensive care unit; INR = international normalized ratio; IVC = inferior vena cava; LMWH = low-molecular-weight heparin; NSAID = nonsteroidal anti-inflammatory drug; P-gp = P-glycoprotein; VTE = venous thromboembolism.

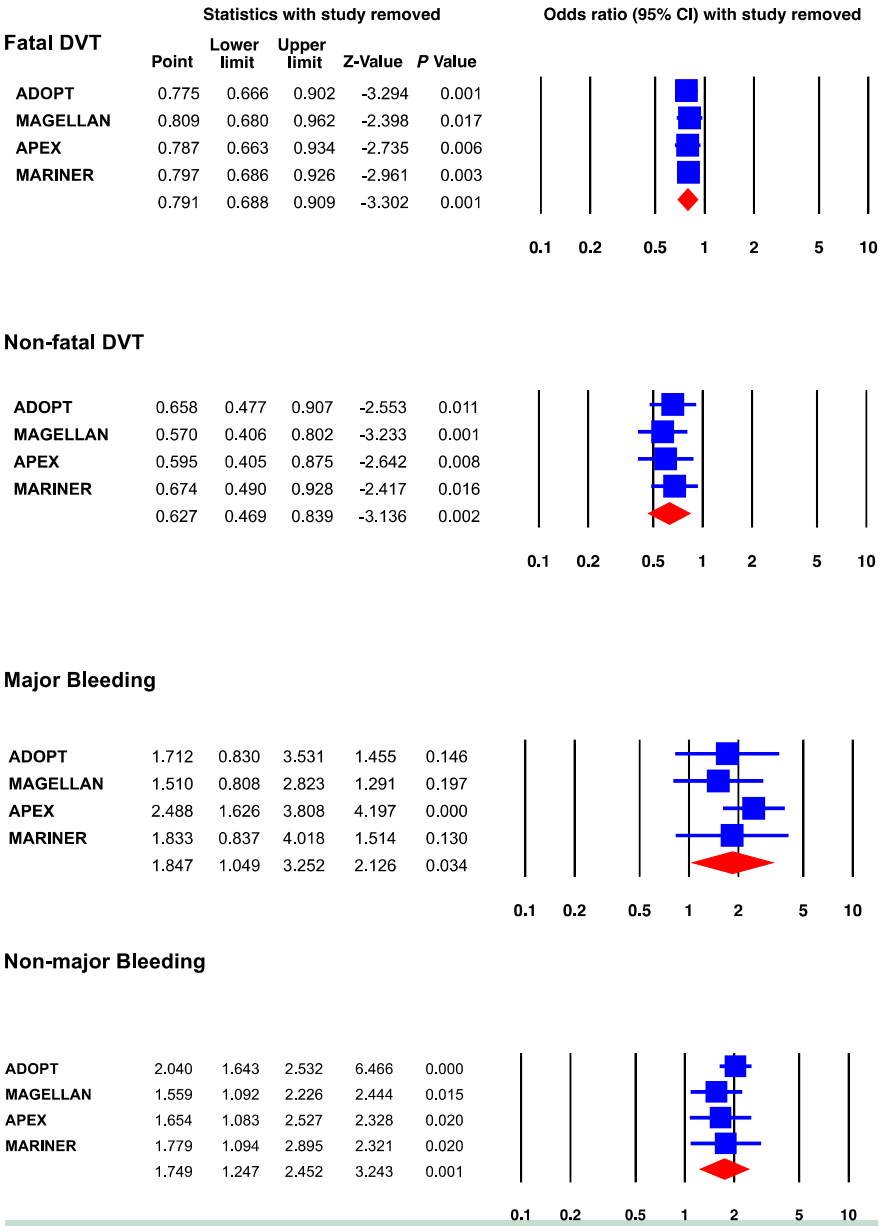
Supplementary Table 5 Cost-Effective Analysis with Formulas Extrapolated to the National Level, per Year

Variable	Formula	Total n
Nationally eligible medically hospitalized patients	36 million annual hospitalizations in the United States, of which 56% are for medical reasons; of those, 25%-30% are eligible for oral thromboprophylaxis (36,000,000 × .56× (0.25 or 0.3)	5,040,0 00-6,048,000
Symptomatic VTE prevented	1 in 247 × Nationally eligible patients for oral thromboprophylaxis	20,401-24,482
Major bleeding events	1 in 453 × Nationally eligible patients for oral thromboprophylaxis	11,130-13,357
Clinically relevant nonmajor bleeding events (CRNMB)	1 in 193 × Nationally eligible patients for oral thromboprophylaxis	25,804-30,965
Fatal bleeding events	1 in 3290 × Nationally eligible patients for oral thromboprophylaxis	1532-1838
Fatal PE prevented	1 in 1069 × Nationally eligible patients for oral thromboprophylaxis	4715-5658
Net number of lives saved	Fatal PE prevented — Fatal bleeding events	3183-3820
Variable	Formula	Cost $
Cost of Preventing one nonfatal symptomatic VTE with rivaroxaban	NNT (247) × 45-day drug cost ($450-$650)	Approximately $111,150-$160,550
Annual National Cost of extended oral thromboprophylaxis	Nationally eligible patients for oral thromboprophylaxis × 45-day drug cost ($450-$650)	Approximately $2.27-3.93 billion dollars annually
Cost saving of prevented symptomatic VTE	24,482 × $10-20,000	$245-490 million (using $15K, ~$367 million)
Cost of major bleeding	13,357 × $15-50,000	$200-668 million (using $30K, ~$401 million)
Cost of CRNMB	30,965 × $1-2000	$31-62 million
Cost of fatal bleeding	1838 × $9.1 million (VSL)	$17 billion
Cost saving of prevented fatal PE	5658 × $9.1 million (VSL)	$51 billion
Total cost of extended thromboprophylaxis	Cost of drug + cost of major bleeding + cost of CRNMB	$4.66 billion dollars annually

NNT = number needed to treat; PE = pulmonary embolism; VSL = value of a statistical life; VTE = venous thromboembolism.



Supplementary Figure 1 Flowchart of data collection.



Supplementary Figure 2 Sensitivity analyses using "one study removed" method evidence for efficacy and safety endpoints.